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Mimic toxicity of Beta-blocker drugs by structural base descriptors

Akshay Tiwari [1], Neel Kamal, Ajit Choubey, V.W. Bhagwat

School of Studies in Chemistry & Biochemistry, Vikram University, Ujjain, MP. India

Abstract: QSAR study has been carried out on the set of 35 Beta-blocker drugs for the modelling of toxicity (Ld50), using topological indices. The stepwise multilinear regression analysis method is used for modelling and the obtained models are critically discussed and examined by various types of cross validation parameters.

Keywords: Beta-Blockers , LD50, topological index, regression analysis.

1. Introduction

Beta-adrenergic antagonists, or commonly referred to as beta-blockers, are important in the management of angina pectoris, hypertension and arrhythmia. The primary function of beta-blockers is to reduce the frequency of anginal episodes and raise the anginal threshold by attenuating the chronotropic and inotropic responses to adrenergic stimulation, thus diminishing myocardial oxygen consumption1.

Chemicals can have a wide range of effects on our health which Depends on how the chemical will be used. In 1927, J.W. Trevan attempted to find a way to estimate the relative poisoning potency of drugs and medicines used at that time. He developed the lethality testing (the LD50tests) by measuring how much of a chemical is required to cause death, because the use of death as a "target" allows for comparisons between chemicals that poison the body in very different ways[2]. To compare the toxic potency or intensity of different chemicals, researchers must measure the same effect. The LD50 gives a measure of the immediate or acute toxicity of a chemical in the strain, sex, and age group of a particular animal species being tested. In general, the smaller the LD50value, the chemical is more toxic[3]. So the use of LD50as a activity in Quantitative Structure Activity Relationship studies has create interest in development of novel and target drugs[4].

The toxicity of beta-blocker drugs has very much importance in medicinal chemistry. The use of topological indices in the modeling of LD50is important stage in QSAR studies[5]. We have used a large set of topological Zm2V13, Connectivity indices (1cAV, 2cAV ,3cAV, 1cV, 3cV, 2c and 0cV)[6-7] and Mean Information Content on the Distance Degree Equality (IDDE)[8] are used as structural descriptors in QSAR studies. The basic assumption of this research work is that the toxicity (Ld50) value of compounds may be related to their structural descriptors as a multi-linear function.

2. Computational Method

LD_{50}: The value of LD_{50} is taken from literature for the set of 35 beta-blocker drugs.

Topological Indices: The topological indices: Zagreb Valence vertex degree index (Zm^2V)[13], Connectivity indices ($^1\chi^{AV}$, $^2\chi^{AV}$,$^3\chi^{AV}$, $^1\chi^{V}$, $^3\chi^{V}$, $^2\chi$ and $^0\chi^{V}$)[6-7] and Mean Information Content on the Distance Degree Equality (IDDE) [8] used in the present investigation were calculated by topological graphs of beta-blocker drugs by deleting carbon hydrogen as well as heteroatom hydrogen bonds from respective molecular structures. The calculations are of those topological indices, which are available in the literature;

[1] Corresponding Authors

e-mail: dr.akstiwariji@gmail.com

therefore the details of their calculations are not needed to be given here.

Statistical Analysis: The regression analysis was performed using maximum-R^2 method in forward direction by the SPSS (11.0) software[18].

Cross Validation: The models having the best correlation potential need not to have the best predictive value too. As opposed to traditional regression methods, the cross-validation method evaluates the validity of a model by how well it predicts data rather than how well it fits data. We have estimated cross-validation parameters, which are presented in table-3, and meanings of some are given below. Indication of the performance of the model is obtained from the cross-validated correlation coefficient R^2_{cv}, which is defined as:

$$R^2_{CV} = 1 - \frac{PRESS}{SSY}$$

PRESS (Predicted Residual Errors Sum of Squares) is the sum of squared difference between the actual and that predicted when the compound is omitted from the fitting process.

$$PRESS = \sum \left(Y_{cal.} - Y_{pre.} \right)^2$$

In addition to PRESS and R^2_{cv}, some parameters are also needed to evaluate the Quality factor (Q). Uncertainty of prediction (S_{PRESS}) Root mean square errors (RMS) and Predictive square error (PSE) are needed to decide predictive potential of the proposed models. The calculation of these parameters is available in the literature, therefore the details are not given here.

3. Results and discussion

Our results, as discussed below, establish that our objective is highly fulfilled. For a set of 35 beta-blocker drugs, we obtained good predictive models[9].The names of 35 beta-blocker drugs are given in Table-1 along with the value of toxicity (Ld_{50}) and topological indices.For the modelling of toxicity (Ld_{50}), we have used maximum-R^2 method in forward direction and finally obtained statistically significant models. In the proposed model, k is the number of structural invariants used in the regression, SE is the standard error of estimation, R is the correlation coefficient, R^2adj is the adjustable R^2, F is the F-statics and Q is the quality factor. Additionally, the predictive potency of the models is the establishment from cross validation analysis using the various cross validation parameters like PRESS (Predicted residual sum of squares), S_{PRESS} (Uncertainty of prediction), R^2_{CV} (Cross validation correlation coefficient) and PSE (Predictive square error).[4]

The topological indices are numerical representation of molecular structure into their molecular structure. They are obtained by transforming molecular structure into its molecular graph via mathematical expression. Such transformation is carried out by deleting all the carbon-hydrogen as well as heteroatom hydrogen bonds in the molecular structure. In chemical graph theory and topology, atoms are treated as vertices and the bonds edges. When certain conditions are imposed on vertices, edges, or both a number is obtained which is called the topological index. Such topological indices used in the modelling of physicochemical properties, biological activity and toxicity of organic compounds[10-16].

The preliminary requirement to use the maximum-R^2 method is to the examination of inter-correlations among molecular descriptors used and their correlation with LD_{50} to be modeled by regression analysis is the basic requirement to use the maximum-R^2 method. The correlation matrix obtained in the present study is given in table-2.The correlation matrix shows that the topological indices ${}^1\chi^{AV}$, ${}^2\chi^{AV}$ and ${}^3\chi^{AV}$, ${}^1\chi^{V}$ and ${}^3\chi^{V}$, and ${}^2\chi$ and ${}^0\chi^{V}$ are highly correlated. Thus, a model containing any combination of these indices may suffer from the defect due to collinearity. To overcome this difficulty we will use the recommendations of Randic[17]. The correlation matrix (Table-2) also shows that none of the molecular descriptors used are capable of modelling $_{LD50}$independently. Thus it can be concluding that step-wise multivariate regression analysis is required to obtain the statistically significant models. Initial multivariate regression analysis indicates that meaningful regression models are obtained when multi parametric regressions with eight or more correlating parameters are used. Among the several parametric models, the one given below is found to be the best. For the aforementioned model, the value of initial statistical parameter is good but not significant for the correlation. Looking to such an excellent result there was no need to attempt for further regression

analysis. However with a hope of obtaining still better results we have carried out several 9-parametric regression analyses and the one yielded significantly improved statistics model-1.

Table 1. Compounds name, log $_{LD50}$value and topological indices for 35 beta-blocker drugs.

SN	Compounds	log LD_{50}	$^{2}\chi$	$^{0}\chi^{A}$	$^{1}\chi^{A}$	$^{0}\chi^{V}$	$^{1}\chi^{V}$	$^{3}\chi^{V}$	$^{1}\chi^{AV}$	$^{2}\chi^{AV}$	$^{3}\chi^{AV}$	Δ_1	Zm^2V	IDDE
1	Alprenolol	2.44	7.247	0.743	0.479	11.225	6.362	2.530	0.353	0.210	0.105	2.268	176	3.614
2	Atenolol	3.30	8.170	0.750	0.472	11.426	6.386	2.506	0.336	0.201	0.104	2.583	207	3.772
3	Amosulalol	2.02	11.351	0.737	0.456	15.622	9.652	4.900	0.357	0.198	0.111	2.673	275	4.023
4	Arotinolol	2.56	10.798	0.741	0.448	15.778	9.840	6.140	0.410	0.274	0.166	0.903	230	4.143
5	Befunolol	2.00	9.244	0.734	0.453	12.550	7.048	3.048	0.320	0.179	0.085	2.921	279	4.011
6	Bupranolol	2.71	8.437	0.764	0.460	12.079	6.409	2.643	0.356	0.235	0.110	1.868	180	3.461
7	Bucumolol	2.83	10.343	0.742	0.446	13.473	7.355	3.266	0.320	0.196	0.088	2.905	289	3.880
8	Bufuralol	1.47	8.831	0.739	0.445	12.156	6.849	2.089	0.342	0.206	0.094	2.055	225	3.471
9	Bunitrolol	3.13	7.995	0.755	0.468	11.104	5.972	2.307	0.332	0.217	0.096	2.449	202	3.572
10	Carazolol	2.12	9.626	0.706	0.444	12.966	7.686	3.685	0.320	0.178	0.086	2.962	278	4.187
11	Cartelol	2.91	9.815	0.736	0.448	12.902	7.326	3.308	0.333	0.267	0.097	2.523	249	3.975
12	Cloranolol	3.11	8.437	0.764	0.460	12.347	6.543	2.740	0.363	0.241	0.114	1.734	178	3.461
13	Esmolol	1.97	8.631	0.746	0.477	12.964	7.209	2.973	0.343	0.202	0.110	2.798	229	3.975
14	Indenolol	2.74	7.700	0.720	0.456	11.018	6.492	2.982	0.342	0.198	0.099	2.113	198	3.837
15	Labetalol	2.06	10.199	0.730	0.459	13.775	8.052	4.039	0.322	0.182	0.104	3.417	279	4.085
16	Levobunolol	3.18	9.709	0.736	0.448	13.109	7.576	3.563	0.344	0.215	0.102	2.290	237	3.975
17	Metipranolol	1.49	9.638	0.766	0.464	14.318	7.554	3.417	0.343	0.196	0.101	2.664	265	3.823
18	Moprolol	2.86	6.867	0.745	0.478	10.642	5.804	2.262	0.341	0.199	0.098	2.326	186	3.735
19	Metoprolol	2.07	7.683	0.741	0.480	12.056	6.736	2.722	0.355	0.214	0.113	2.377	185	3.827
20	Nadolol	3.65	10.323	0.742	0.446	13.542	7.788	3.816	0.339	0.213	0.103	2.472	240	3.971
21	Nifenalol	2.27	6.867	0.758	0.469	9.382	5.162	2.208	0.586	0.323	0.187	2.341	205	3.203
22	Nadoxolol	2.26	7.831	0.719	0.460	10.360	5.955	2.754	0.298	0.163	0.086	3.248	253	4.037
23	Nipradilol	1.87	10.077	0.731	0.456	13.228	7.555	3.350	0.315	0.179	0.091	3.397	327	4.350
24	Oxprenanol	2.57	7.601	0.741	0.481	11.634	6.501	2.399	0.342	0.199	0.096	2.629	204	3.827
25	Pindolol	2.37	7.601	0.741	0.481	11.634	6.501	2.748	0.330	0.189	0.092	2.629	212	3.837
26	Penbutolol	3.09	9.535	0.728	0.453	13.562	8.104	4.013	0.368	0.237	0.122	1.851	202	3.975
27	Pronethalol	2.71	7.326	0.721	0.454	10.350	6.067	2.878	0.337	0.195	0.099	2.098	183	3.735
28	Practolol	2.46	8.170	0.750	0.472	11.642	6.390	2.379	0.613	0.336	0.197	2.579	215	3.722
29	Propanolol	2.75	8.053	0.719	0.458	11.466	6.686	2.943	0.334	0.193	0.095	2.479	214	3.932
30	Toliprolol	3.12	6.792	0.748	0.473	10.234	5.686	2.194	0.355	0.217	0.110	1.889	159	3.500
31	Tertatolol	2.08	9.181	0.729	0.450	13.425	8.247	4.444	0.393	0.255	0.139	1.208	193	3.446
32	Timolol	3.08	9.535	0.728	0.453	13.650	7.897	3.535	0.359	0.221	0.107	2.058	233	3.749
33	Tilisolol	3.14	10.226	0.742	0.447	13.589	7.420	3.353	0.323	0.199	0.088	2.857	274	3.880
34	Sotalol	3.41	8.494	0.764	0.460	11.660	7.661	2.925	0.426	0.253	0.122	0.616	152	3.419
35	Xibenolol	2.76	8.309	0.764	0.461	12.079	6.414	2.854	0.356	0.232	0.114	1.880	181	3.572

log LD_{50}= -7.050 +1.243* **x2+**15.209* **x1a**-0.591* **x0v** +2.024 * **IDDE** -0.025* **Zm2v**-0.385 ***AECC +0**.094* **IAC**-0.870* **x1v+0**.239* **x3v.**

k = 9, **SE** =0.257, **R** = 0.843, **F** =14.804, **Q** = 3.65 , $\mathbf{R^2_{CV}}$ = 0.81279

Table 2. Correlation matrix

	LD_{50}	$^{2}\chi$	$^{0}\chi^{A}$	$^{1}\chi^{A}$	$^{0}\chi^{V}$	$^{1}\chi^{V}$	$^{3}\chi^{V}$	$^{1}\chi^{AV}$	$^{2}\chi^{AV}$	$^{3}\chi^{AV}$	Δ_1	Zm^2V	IDDE
LD_{50}	1.00												
$^{2}\chi$		1.00											
$^{0}\chi^{A}$		–0.17	1.00										
$^{1}\chi^{A}$		–0.71	0.38	1.00									
$^{0}\chi^{V}$		0.93	–0.08	–0.51	1.00								
$^{1}\chi^{V}$		0.89	–0.22	–0.54	0.94	1.00							
$^{3}\chi^{V}$		0.79	–0.29	–0.54	0.84	0.92	1.00						
$^{1}\chi^{AV}$		–0.21	0.34	0.19	–0.19	–0.13	–0.09	1.00					
$^{2}\chi^{AV}$		–0.09	0.43	0.05	–0.07	–0.02	0.02	0.89	1.00				
$^{3}\chi^{AV}$		–0.09	0.32	0.15	–0.02	0.05	0.15	0.93	0.90	1.00			
Δ_1		0.13	–0.32	0.08	–0.00	–0.16	–0.18	–0.31	–0.51	–0.42	1.00		
Zm^2V		0.71	–0.38	–0.47	0.56	0.46	0.40	–0.28	–0.37	–0.30	0.70	1.00	
IDDE		0.57	–0.59	–0.28	0.52	0.52	0.52	–0.45	–0.49	–0.36	0.55	0.74	1.00

Table 3. Cross- validation parameters for the proposed models

Model	No. of Parameters	PRESS	PSE	R^2_{CV}	S_{PRESS}	Q
1	9	1.57	0.01235	0.8769	0.2233	4.225
2	11	1.40	0.01588	0.8364	0.2473	3.7468
3	12	1.09	0.01780	0.81279	0.2513	3.651

Addition of the parameter $^{1}\chi^{V}$ during the stepwise regression analysis yielded a 10-parametric regression expression with improved statistics.

The significant improvement in the statistics indicates its favorable role in the modelling of lipophilicity. When some new indices are interchanged to eq.1, great improvements are observed in the statistics. No other topological index yields such an improvement in the statistics; the resulted 11-parametric model is given as below model-2:

log Ld_{50}= -14.699 + 2.975* **x2+**105.657 **x1a-**0.418* **x0v+0**.760* IDDE-.0016* **Zm2v**-2.604* **x1v+0**.881* **x3v**-43.572* **x0a**-37.031* **x3av**+12.306* **x1av**-1.732* **Del1. (2)**

k = 11**, SE** = 0.240, **R** = 0.9268**, Q**= 3.746, **F** = 40.364 **, R^2_{CV}** = 0.8364

Successive regression analysis resulted into a 12-parametric model having the best statistics than those described above. These obtained excellent model found is given as below model-3:

log Ld_{50}= -15.142+3.644***X2+**128.907***X1a-**0.383***X0v+ **0**.746***IDDE**-0.017* **Zm2v**-3.295* **X3v +0**.904* **X3v**-56.504* **X0a**-32.013* **X3av+**15.471* **X1av**-2.302* **Del1**-10.319* **x2av. (3)**

k = 12**, SE** = 0.2233**, R** = 0.9437**, Q**=4.225**, F** = 41.955 **, R^2_{CV}** = 0.8769

The consisting parameters of model–3 have both negative and positive contribution in the modelling of lipophilicity. The initial statistics SE, R, Q and F indicate that the model 3 (eq 3) is found to be far superior than the other proposed models based on eq 1, 2 and 3.The aforementioned results can be further established by estimating and comparing quality factor. This quality factor Q is defined by the ratio of the correlation coefficient (R) to the standard error of estimation (SE). That is Q = R/SEE. For the model-3, the value of Q is 4.2, which is greater than other proposed model expressed by eq 1-3 respectively.

We have estimated cross validation parameters to explain our results. The meaning of these parameters is given in experimental section and their values are recorded in Table 3. PRESS is a good estimate of the real prediction error of the model. If PRESS is smaller than the model predicts better than chance and can be considered statistically significant. In this regard, all the models proposed by us (table-3) are good and model 3 is the best one. S_{PRESS} is another cross-validation parameter and is a measure of uncertainty of prediction. However, in our case S_{PRESS} is found to be the same as that of SE, thus the both these parameters carry same meaning and use of S_{PRESS} is useless. In such case we have still

another cross validation parameter named as predictive square error (PSE). This parameter is more directly related to uncertainty of prediction. The lowest value of PSE (Table 3) for the model-5 expressed by eq 5, supports its highest predictive potential.

Finally, the predictive potential of the model is confirmed by calculating predictive correlation coefficient of the model (R^2_{pred}), (Fig. 1) 0.8905, for the expressed model-3 (eq 3). Thus R^2_{pred} (0.8905) indicates that our improved model as expressed by eq. 3 is the best.

As discussed above, it is accomplish that models obtained by combination of topological indices have better quality and predictivity. The obtained model has very much potential for the prediction of properties of selected drugs. Predictive QSAR/ QSAR models which are based on molecular descriptors have been proposed in this study to correlate the toxicity of compounds. Application of the developed model to a testing set of 35 compounds demonstrates that the new model is reliable with good predictive accuracy and simple formulation.

Since the QSAR/ QSAR were developed on the basis of theoretical molecular descriptors calculated exclusively from molecular structure, the proposed model could potentially provide useful information about the activity/toxicity of drug compounds.

We have developed here a useful QSAR/QSTR equation derived from theoretical descriptors (Topological Index). A MLR is successfully presented for prediction the toxicity (log Ld_{50}) of various 35 drug compounds with diverse chemical structures using a linear quantitative structure-toxicity relationship. A model with high statistical quality and low prediction errors was obtained.

The macroscopic (bulk) activities/properties of chemical compounds clearly depend on their microscopic (structural) characteristics. Development of quantitative structure property/ toxicity relationships (QSAR/QSTR) on theoretical descriptors is a powerful tool not only for prediction of the chemical, physical and biological properties/activities of compounds, but also for deeper understanding of the detailed mechanisms of interactions in complex systems that predetermine these properties/activities.

MLR analysis provided useful equation that can be used to predict the log LD_{50} of chemicals based upon Topological Index parameters. The results indicate that a strong correlation exists between the log LD_{50} and Topological Index for drug compounds. This procedure allowed us to achieve a precise and relatively fast method for activity determination of different series of drug compounds and to predict with sufficient accuracy of new drug derivatives. All these results, therefore, suggests that the estimated activity of the unknown compounds is well justified.

4. Conclusions

Predictive QSAR models which are based on molecular descriptors have been proposed in this study to correlate the toxicity of compounds. Application of the developed model to a testing set of 35 compounds demonstrates that the new model is reliable with good predictive accuracy and simple formulation. Since the QSAR/QSTR was developed on the basis of theoretical molecular descriptors calculated exclusively from molecular structure, the proposed model could potentially provide useful information also about the activity of drug compounds as lower the toxicity higher the activity. We have developed here a useful QSAR/QSTR equation derived from theoretical descriptors (Topological Index).

MLR is successfully presented for prediction the toxicity (logLD50) of 35 drug compounds with diverse chemical structures using a linear quantitative structure- toxicity relationship. A model with high statistical quality and low prediction errors was obtained. The macroscopic (bulk) activities/ toxicity of chemical compounds clearly depend on their microscopic (structural) characteristics. Development of quantitative structure property/activity/toxicity relationships (QSPR/QSAR/QSTR) on theoretical descriptors is a powerful tool not only for prediction of the chemical, physical and biological properties/activities/toxicity of compounds, but also for deeper understanding of the detailed mechanisms of interactions in complex systems that predetermine these properties. MLR analysis provided useful equation that can be used to predict the logLD50 of chemicals based upon Topological Index parameters. The results indicate that a strong correlation exists between the logLD50 and Topological Index for drug compounds. This procedure allowed us to achieve a precise and relatively fast method for activity determination of different series of drug compounds and to predict with sufficient accuracy of new drug derivatives. All these results, therefore, suggests that the estimated toxicity of the unknown compounds will be justified.

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