Use Of Balaban Index, Zagreb's Index And Kier & Hall's Valency Connectivity Indices In Modeling Cardiotonic Agents- Cardio-Selective β-Blockers

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Abstract: We have attempted to develop Quantitative Structure Activity Relationship (QSAR) to predict Cardiotonic Activity of Cardio-selective β-blockers. The results have shown that Cardiotonic activity of Cardio-selective β-blockers can be modeled excellently in tri-parametric models in which Balaban Index F, Zagreb Group index-M1 and Kier & Hall's zero-order valency connectivity index played a dominating role. The predictive ability of the models is discussed on the basis of cross-validation method. The superiority of these indices over several other topological indices is critically examined. The values obtained for the best model are- R2 = 0.8634, Adjusted R2= 0.5913, Coefficient of variation= -1.3450 and F-ratio= 9.197.

Keywords: Cardiotonic agents, Cardio-selective β-blockers, Topological indices, Balaban Index, Zagreb's Group Index, Valency Connectivity Index.

1. Introduction:

Cardiotonic agents viz., cardiotonics are the drugs that act on the myocardium and increase the force of myocardial contraction and thus are of great value in the treatment of heart failure. It is worth mentioning that such an increase in the force of myocardial contraction is called positive Inotropic effect[1-3]. The increase in the force of myocardial contraction leads to increased cardiac output, decreased heart size, venous pressure and blood volume, dieresis and relief of edema in patients with heart failure. In addition, cardiotonics also slow down the ventricular rate in arterial fibrillation and flutter[1-5]. Cardiotonic agents are the agents that have a strengthening effect on the heart or that can increase the force of contraction of heart without increasing actual oxygen consumption.

In the present study we have chosen cardio-selective β-blocker (Figure 1) because they exhibit interesting biological and chemical properties like Cardiotonic activity and may eventually lead to useful applications. Several molecular modeling using uni- as well as multivariate analyses were made using NCSS software. Our present paper is based on the studies of Cardio-selective β- blockers. Cardio-selective β- blockers are a common type of high blood-pressure medicines and are also used to treat problems such as irregular heart-beat, angina and symptoms of anxiety. They are particularly used for the management of cardiac arrhythmias, cardio-protection after myocardial infarction (heart attack) and hypertension [6]. As beta adrenergic receptor antagonists, they diminish the effects of epinephrine (adrenaline) and other stress hormones. Beta adrenergic blocking agents prevent stimulation of the beta adrenergic receptors at the nerve endings of the sympathetic nervous system and therefore decrease the activity of the heart. They block sympathetic stimulation of the heart and reduce systolic pressure, heart rate, cardiac contractility and output, so decrease myocardial oxygen demand and increase exercise tolerance. Cardioselective β-blockers are beneficial in the reduction of mortality in patients with Chronic Obstructive Pulmonary Disease (COPD)[7] undergoing vascular surgery, with an intensified dosage being most effective.

The objective of the present paper is to derive a relation between the structure of a series of compounds- cardio-selective β-blockers and the activity of these compounds, which is known as QSAR model[8-13]. This model could improve lead-optimization techniques for finding potential drugs to treat heart related diseases.

The different topological indices[14-22] are calculated in QSAR viz. Weiner index (W)[23], Platt's index (P)[24-26], Schultz molecular topological index (SMTI)[27,28], Topological index (T), Balaban Indices- J, F and G[29]; Zagreb's group Indices- M_1 and M_2[30]; Randic's Connectivity Indices- ${}^0\chi$, ${}^1\chi$, ${}^2\chi$ and ${}^3\chi$[31-34]; and Kier & Hall's Valency Connectivity Indices- ${}^0\chi^v$, ${}^1\chi^v$, ${}^2\chi^v$ and ${}^3\chi^v$[35,36].

The series of cardio-selective β- blockers which we have taken into consideration in this paper has the skeleton structure as:

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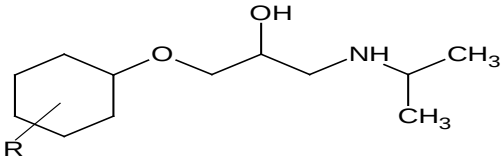
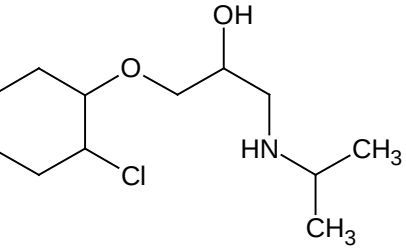
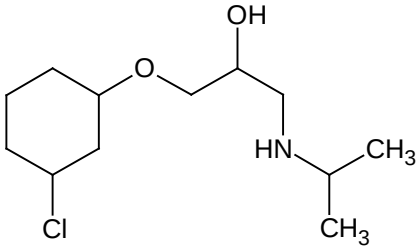
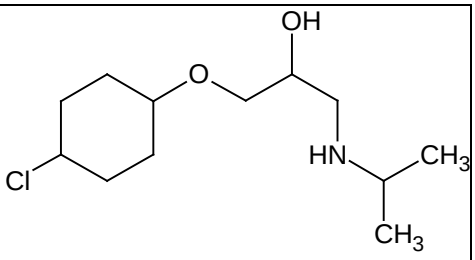
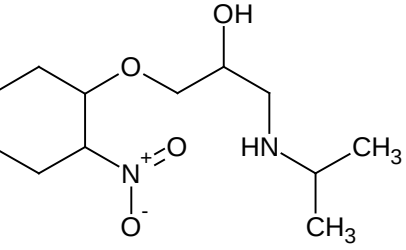
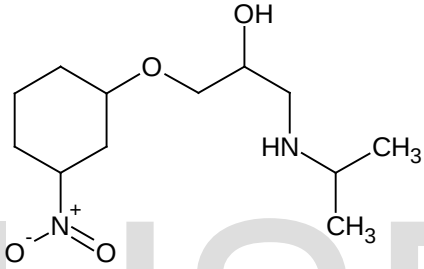
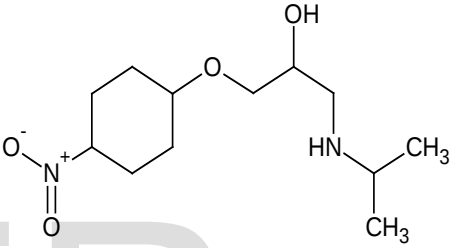
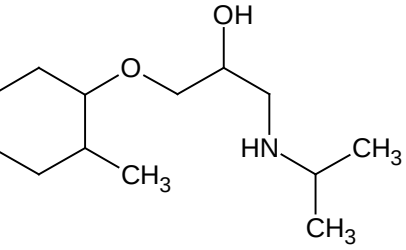
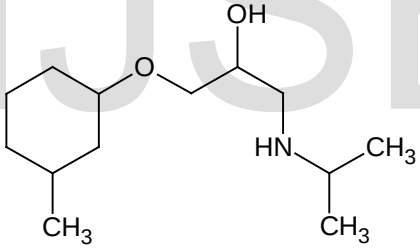
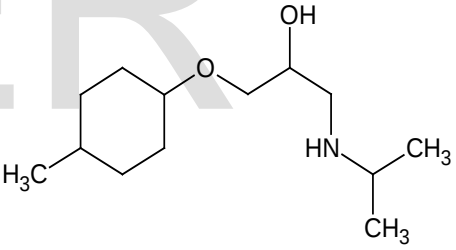
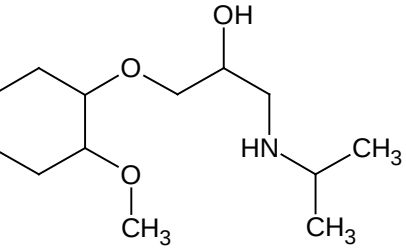
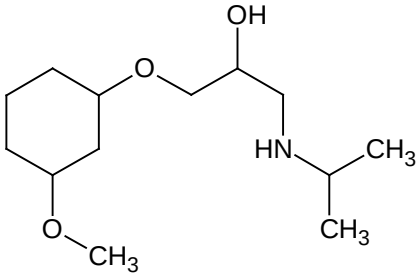
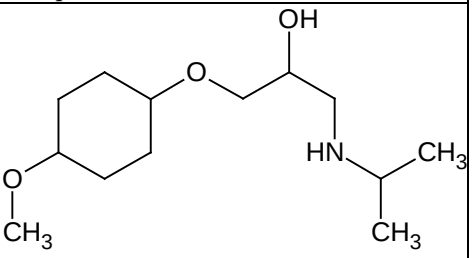
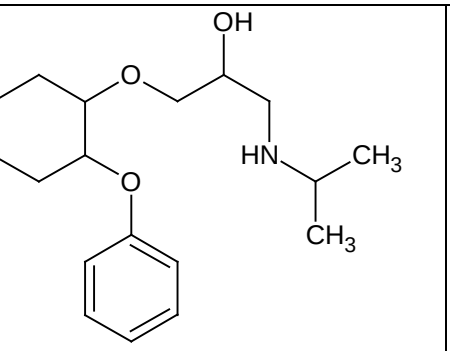


In this compound, the substituent group R is varied by taking various different substituent at different positions i.e. ortho, meta and para and their activities are taken from the literature (from the work of Khadikar et al). The whole series of compounds is tabulated below:

Fig. 1 Skeleton of cardio-selective β -blocker

Table-1: Structural details of the Cardio-selective β-blockers under study

 Compound no. 1	 Compound no. 2	 Compound no. 3
 Compound no. 4	 Compound no. 5	 Compound no. 6
 Compound no. 7	 Compound no. 8	 Compound no. 9
 Compound no. 10	 Compound no. 11	 Compound no. 12



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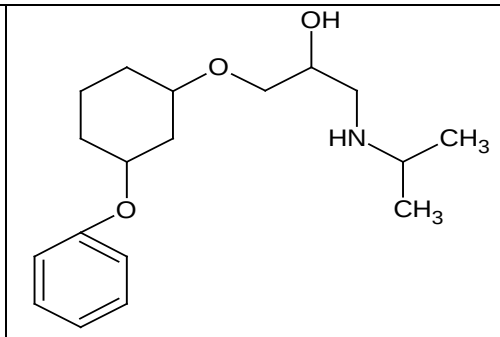

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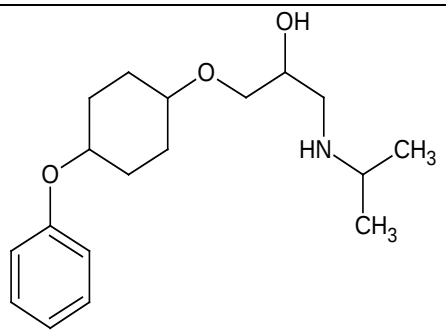

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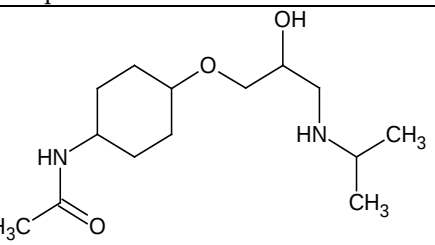

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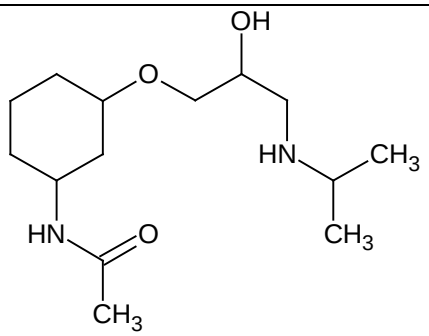

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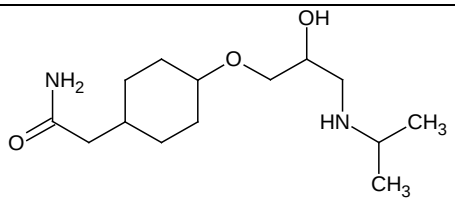

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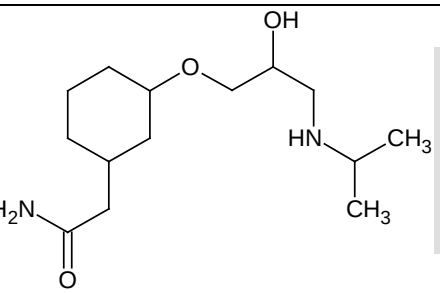

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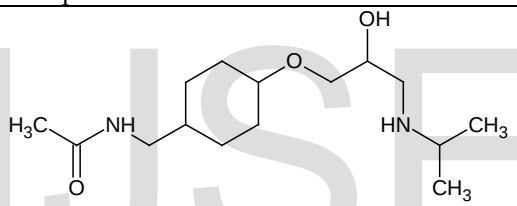

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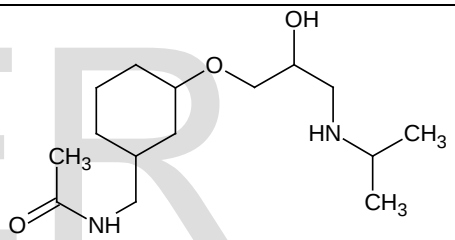

Compound no. 21

Quantitative structure–activity relationship (QSAR) methodology can be helpful in correlating the structure of a large series of drug compounds with its activity. Mathematical models are formed that correlate molecular structure to an activity or property of interest. Molecular structure is encoded through the generation of the descriptions which are numerical values corresponding to topological and connectivity indices. Quantitative structure–activity relationship (QSAR) methodology is of great importance in modern chemistry and biochemistry. To obtain a significant correlation, it is essential that appropriate descriptors are employed, whether they are theoretical, empirical or derived from readily available experimental characteristics of structures.

2. Results and Discussion:

Molecular modeling techniques for the group of 21 Cardio-selective β-blockers were considered. Structural details of this set of 21 compounds are given in Table-1. The log of Cardiotonic Activity [log(CA)] of these compounds along with the selected topological indices: Balaban indices F and G; Topological index T; Zagreb group index M_1 and Kier and Hall's valency connectivity indices ${}^0X^v$, ${}^1X^v$, ${}^2X^v$ and ${}^3X^v$ are presented in Table-2. Further details on these molecular descriptors are provided in footnotes of this table.

To decide which topological indices are useful for proposing appropriate model for modeling the activity, we performed variable selection in multiple regression analysis [37]. This helped us to set up the best combination of descriptors and thus propose the best model. This procedure adopted by us also helps us to arrive at the optimal model complex in predicting a response variable

by a reduced set of descriptors out of the larger pool, which are not highly inter-correlated.

The inter-correlation among the descriptors and their correlation with cardiotonic activity is demonstrated by the construction of a correlation matrix (Table-4).

Table-2 Calculated molecular descriptors for the compounds used in the present study

Compound No.	log(CA)	F	G	T	M_1	$^0X^v$	$^1X^v$	$^2X^v$	$^3X^v$
1	0.699	4.242	60.04	32	72	11.04	6.7	5.45	3.386
2	-0.284	4.164	59.22	32	72	11.04	6.684	5.553	3.245
3	-1.0706	4.096	58.25	32	72	11.04	6.684	5.541	3.326
4	0.301	4.538	73.52	36	82	11.17	6.669	5.226	3.203
5	-0.4089	4.354	70.53	36	82	11.17	6.652	5.278	3.183
6	-1.5528	4.198	68.01	36	82	11.17	6.652	5.266	3.228
7	0.233	4.242	60.04	32	72	10.91	6.623	5.35	3.297
8	-0.1805	4.164	59.22	32	72	10.91	6.606	5.444	3.174
9	-1.0458	4.096	58.25	32	72	10.91	6.606	5.432	3.249
10	0.233	4.372	66.5	34	76	11.32	6.69	5.147	3.209
11	-0.041	4.238	64.46	34	76	11.32	6.673	5.196	3.197
12	-0.2676	4.122	69.7	34	76	11.32	6.673	5.185	3.241
13	0.301	4.4	67	40	92	14	7.8	6.3	3.7
14	-0.5229	4.3	79	40	92	15	7.8	6.4	3.8
15	-3	4.4	67	40	92	14	7.9	6.3	3.8
16	-0.1024	4.172	71.72	38	86	12.32	7.272	5.724	3.368
17	-0.1308	4.346	74.71	38	86	12.32	7.272	5.736	3.32
18	-0.6383	4.172	71.72	38	86	12.1	7.284	5.863	3.57
19	-0.6576	4.346	74.71	38	86	12.1	7.284	5.875	3.511
20	-0.4949	4.136	75.2	38	90	13.02	7.745	6.13	3.72
21	0.4685	4.32	78.55	38	90	13.02	7.745	6.142	3.66

F & G= Balaban indices, T= Topological index, M_1= Zagreb Group-1 index, $^0X^v$= Kier and Hall's zero-order valency connectivity index, $^1X^v$= Kier and Hall's first-order valency connectivity index, $^2X^v$= Kier and Hall's second-order valency connectivity index, $^3X^v$= Kier and Hall's zero-order valency connectivity index.

Table-3 Selection result section

Model Size	Decoded Variables	R-Squared	R-Squared Change
1	F	0.240140	0.240140
2	F, T	0.296914	0.056774
3	F, M_1, $^0X^v$	0.663384	0.366469
4	F, M_1, $^1X^v$, $^2X^v$	0.706786	0.043403
5	F, T, M_1, $^1X^v$, $^2X^v$	0.708618	0.001831
6	F, G, T, M_1, $^1X^v$, $^2X^v$	0.709798	0.001181
7	F, T, M_1, $^0X^v$, $^1X^v$, $^2X^v$, $^3X^v$	0.717188	0.007390
8	F, G, T, M_1, $^0X^v$, $^1X^v$, $^2X^v$, $^3X^v$	0.720910	0.003722

Table-4 Correlation- regression report of the Cardiotonic activity of cardio-selective β-blockers

Log(CA)	F	G	T	M_1	$^0X^v$	$^1X^v$	$^2X^v$	$^3X^v$

Log(CA)	1.000000								
F	0.490041	1.000000							
G	0.117533	0.483572	1.000000						
T	-0.051333	0.350613	0.946893	1.000000					
M_1	-0.030200	0.322815	0.948022	0.984392	1.000000				
$^0X^v$	0.109044	0.085269	0.816311	0.845392	0.890534	1.000000			
$^1X^v$	0.093642	0.040702	0.755131	0.799819	0.855457	0.985808	1.000000		
$^2X^v$	-0.018311	-0.143999	0.507645	0.598549	0.670311	0.851082	0.922409	1.000000	
$^3X^v$	0.049120	-0.117858	0.546141	0.591001	0.670104	0.840468	0.903784	0.913805	1.000000

The cardiotonic activity shown in Table-2 is tested in mono, bi and tri-parametric regression analyses.

As expected, Table-5 shows that in mono-parametric correlations, all indices lead to poorer correlations except Balaban index F. The best model obtained among these mono-parametric correlations is Model-1.

Log(CA)= -10.4380 + 2.3971 * F (1)

Table-5 Mono-parametric correlations between 8 parameters and log of Cardiotonic activity [log(CA)]

Model	Parameter	R^2	R^2A	SE	F-ratio
1	F	0.2401	0.1926	-1.8902	5.057
2	G	0.0138	0.0000	-2.1534	0.224
3	T	0.0026	0.0000	-2.1656	0.042
4	M_1	0.0009	0.0000	-2.1675	0.015
5	$^0X^v$	0.0119	0.0000	-2.1555	0.193
6	$^1X^v$	0.0088	0.0000	-2.1589	0.142
7	$^2X^v$	0.0003	0.0000	-2.1681	0.005
8	$^3X^v$	0.0024	0.0000	-2.1658	0.039

The next step was to proceed to bi-parametric correlations associating one of the distance based indices (F,G,T, M_1) with each other as well as Kier & Hall's valency connectivity indices ($^0\chi^v$, $^1\chi^v$, $^2\chi^v$ and $^3\chi^v$). In Table-6, we present the results for bi-parametric correlations involving these pair-wise associations. It is evident that model 9 involving F & T has the highest R^2 value, highest R^2A value, highest F-ratio value and the lowest standard error.

Log(CA)= -10.3025 + 2.8335 * F - 5.6733E-02 * T (2)

Table-6 Bi-parametric models

Model	Parameter	R^2	R^2A	SE	F-ratio
9	F,T	0.2969	0.2032	-1.8779	3.167
10	F,M_1	0.2798	0.1837	-1.9007	2.913
11	F, $^0X^v$	0.2447	0.1440	-1.9464	2.430
12	F,$^1X^v$	0.2456	0.1450	-1.9452	2.441
13	F,$^2X^v$	0.2429	0.1420	-1.9486	2.407
14	F,$^3X^v$	0.2517	0.1520	-1.9373	2.523
15	G,T	0.2696	0.1722	-1.9140	2.768
16	G, $^0X^v$	0.0143	0.0000	-2.2235	0.109
17	G,$^1X^v$	0.0139	0.0000	-2.2240	0.105
18	G,$^2X^v$	0.0220	0.0000	-2.2148	0.169
19	G,$^3X^v$	0.0141	0.0000	-2.2237	0.108
20	G, M_1	0.2119	0.1068	-1.9882	2.017

The next step consist in looking at tri-parametric correlations involving two from the distance based indices (F,G,T, M_1) and one of the Kier & Hall's valency connectivity indices ($^0\chi^v$, $^1\chi^v$, $^2\chi^v$ and $^3\chi^v$). Results are displayed in Table-7. This indicated the occurrence of the best tri-parametric model containing F, M_1 & $^0X^v$ as there was a high improvement in statistics.

$$Log(CA)= -21.9765 + 4.4321 * F - 0.1444 * M_1 + 1.2432 * {}^0X^v \quad (3)$$

$R^2 = 0.6634$, Adjusted $R^2= 0.5913$, Coefficient of variation= -1.3450 and F-ratio= 9.197

Table-7 Tri-parametric models

Model	Parameter	R^2	R^2A	SE	F-ratio
21	F, G, $^0X^v$	0.4238	0.3058	-1.7528	3.496
22	F, T, $^0X^v$	0.6188	0.5371	-1.4312	7.576
23	**F, M_1, $^0X^v$**	**0.6634**	**0.5913**	**-1.3450**	**9.197**
24	F, M_1, $^1X^v$	0.5848	0.4958	-1.4938	6.572
25	F, M_1, $^2X^v$	0.3818	0.2488	-1.8234	2.877
26	F, M_1, $^3X^v$	0.4333	0.3118	-1.7452	3.568
27	F, G, $^1X^v$	0.3801	0.2473	-1.8252	2.861
28	F, G, $^2X^v$	0.2959	0.1451	-1.9452	1.961
29	F, G, $^3X^v$	0.3377	0.1958	-1.8866	2.379
30	F, T, $^1X^v$	0.5508	0.4545	-1.5537	5.722
31	F, T, $^2X^v$	0.3916	0.2613	-1.8081	3.004
32	F, T, $^3X^v$	0.4321	0.3104	-1.7469	3.551

Table-8 QSAR models for Cardiotonic activity of Cardio-selective β-blockers

QSAR Model No.	QSAR Models Log(Cardiotonic Activity)=
1	-10.4380 + 2.3971 * F
2	-0.9415 + 9.8874E-03 * G
3	0.1261 - 1.1446E-02 * T
4	-7.0275E-02 - 2.5704E-03 * M_1
5	-1.2912 + 8.7904E-02 * $^0X^v$
6	-1.2129 + 0.1357 * $^1X^v$
7	-8.9797E-02 - 3.3398E-02 * $^2X^v$
8	-0.8365 + 0.1684 * $^3X^v$
9	-10.3025 + 2.8335 * F - 5.6733E-02 * T
10	-10.4240 + 2.7292 * F - 1.7900E-02 * M_1
11	-10.9499 + 2.3689 * F + 5.4617E-02 * $^0X^v$
12	-11.1155 + 2.3824 * F + 0.1069 * $^1X^v$
13	-11.1356 + 2.4347 * F + 9.7327E-02 * $^2X^v$

14	-11.9431 + 0.3715 * $^{3}X^{v}$ + 2.4596 * F
15	2.8813 + 0.1352 * G - 0.3507 * T
16	-1.1257 + 7.1911E-03 * G + 3.1653E-02 * $^{0}X^{v}$
17	-1.0068 + 9.1648E-03 * G + 1.6479E-02 * $^{1}X^{v}$
18	-0.1846 + 1.4374E-02 * G - 0.1916 * $^{2}X^{v}$
19	-0.7624 - 7.3607E-02 * $^{3}X^{v}$ + 1.0874E-02 * G
20	0.9907 + 0.1214 * G - 0.1190 * M_1
21	-21.8991 + 4.5472 * F - 8.9838E-02 * G + 0.7268 * $^{0}X^{v}$
22	-18.5745 + 4.2132 * F - 0.2997 * T + 0.9445 * $^{0}X^{v}$
23	**-21.9765 + 4.4321 * F - 0.1444 * M_1 + 1.2432 * $^{0}X^{v}$**
24	-21.5066 + 4.2925 * F - 0.1152 * M_1 + 1.7616 * $^{1}X^{v}$
25	-16.9388+ 3.7140 * F- 0.05198 * M_1 + 0.9127 * $^{2}X^{v}$
26	-18.7253 + 2.0568 * $^{3}X^{v}$ + 3.8243 * F - 5.8276E-02 * M_1
27	-19.7213 + 4.1004 * F - 6.5135E-02 * G + 0.9333 * $^{1}X^{v}$
28	-15.3906 + 3.4158 * F - 0.0297 * G + 0.4767 * $^{2}X^{v}$
29	-17.9197 + 1.3468 * $^{3}X^{v}$ + 3.7241 * F - 3.9135E-02 * G
30	-18.3769 + 4.0743 * F - 0.2421 * T + 1.3445 * $^{1}X^{v}$
31	-15.8262 + 3.6933 * F - 0.1286 * T + 0.7946 * $^{2}X^{v}$
32	-17.1209 + 1.7309 * $^{3}X^{v}$ + 3.7490 * F - 0.1379 * T

In Table-9, we present the Actual & Predicted log(CA) values together with the residuals, obtained via Eq. 3, i.e. Model-23. Figure-2 displays a plot of these values and the linear correlation obtained there from.

Table-9 Actual and Predicted values of log(CA) and residuals using Eq. (3), i.e. Model 23

Compound No.	Actual log(CA)	Predicted log(CA)	Residual
1	0.699	0.157	0.542
2	-0.284	-0.189	-0.095
3	-1.071	-0.490	-0.580
4	0.301	0.187	0.114
5	-0.409	-0.629	0.220
6	-1.553	-1.320	-0.233

7	0.233	-0.008	0.241
8	-0.181	-0.354	0.174
9	-1.046	-0.655	-0.390
10	0.233	0.498	-0.265
11	-0.041	-0.096	0.055
12	-0.268	-0.610	0.343
16	-0.102	-0.589	0.487
17	-0.131	0.182	-0.313
18	-0.638	-0.858	0.219
19	-0.658	-0.087	-0.571
20	-0.495	-0.447	-0.048
21	0.469	0.368	0.100

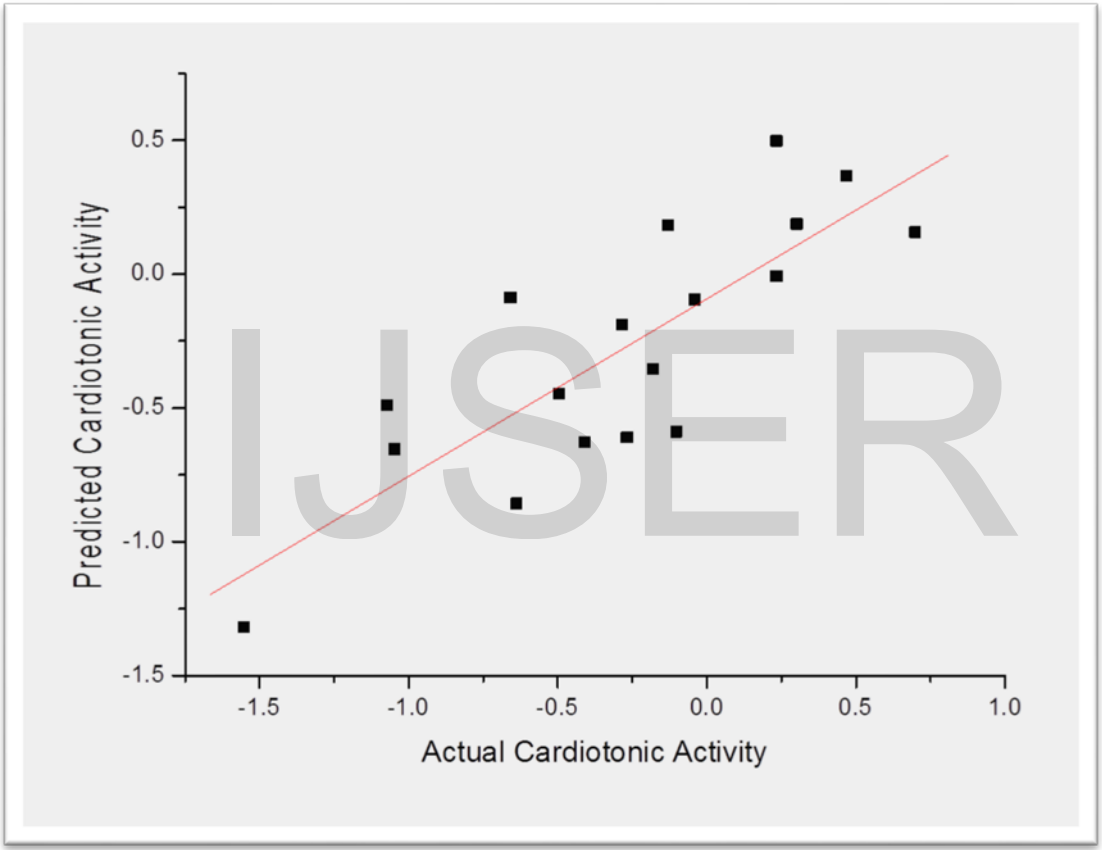

Fig. 2 A plot between Actual & Predicted log(CA) using Eq. (3), i.e. Model 23

Log(CA) = -0.09235 + 0.66323 * X

R= 0.81444 SD= 0.2813

2.1 On the occurrence of colinearity

At this stage, it is worth examining the occurrence or otherwise of colinearity in the proposed models. The best candidate for this purpose would obviously be the tri-parametric model. This we can do in two different ways: (i) by examining the correlation matrices for the two-, three- and four-parameteric models and/or (ii) by calculating VIF for each of the parameters in the model [38]. The correlation matrices for the tri-parametric model is given in Table 10 showing that this model does not suffer from defect of colinearity. To confirm this finding, we calculated VIF, which is a measure of multicollinearity, for each of the parameters involved in both these models.

The VIF is defined as 1/(1)Ri 2), where Ri is the multiple correlation coefficient of the ith independent variable on all

of the other independent variables. A VIF 10 or more (no upper limit is defined) for large data sets indicates a collinearity problem. For small data sets, even VIFs of five or more (here also no upper limit is defined) can signify collinearity. The variables with a high VIF are candidates for exclusion from the model. The VIF values for tri-parametric model are presented in Tables 11. These tables also record the values of yet another parameter called tolerance. This is also a parameter used for investigating collinearity problem. It is just the denominator of VIF. As can be seen from this table, the VIF values of all parameters are less than 10. Statistically, therefore, multicollinearity is not a problem with these models. Now, all the correlating parameters have VIF <10 and thus there is no colinearity problem.

Table-10 Correlation Matrix for best tri-parametric model (i.e Model 23)

	Log(CA)	**F**	**M_1**	**$^0X^v$**
Log(CA)	1.000000			
F	0.490041	1.000000		
M_1	-0.030200	0.322815	1.000000	
$^0X^v$	0.109044	0.085269	0.890534	1.000000

Table-11 Least Squares Multicollinearity Section

Independent Variable	**Variance Inflation**	**R-Squared Vs Other X's**	**Tolerance**
F	1.4322	0.3018	0.6982
M_1	6.8704	0.8544	0.1456
$^0X^v$	6.1995	0.8387	0.1613

Since all VIF's are less than 10, multicollinearity is not a problem.

Table-12 Eigenvalues of Correlations

No.	**Eigenvalue**	**Incremental Percent**	**Cumulative Percent**	**Condition Number**
1	1.977091	65.90	65.90	1.00
2	0.945622	31.52	97.42	2.09
3	0.077287	2.58	100.00	25.58

All Condition Numbers less than 100. Multicollinearity is NOT a problem.

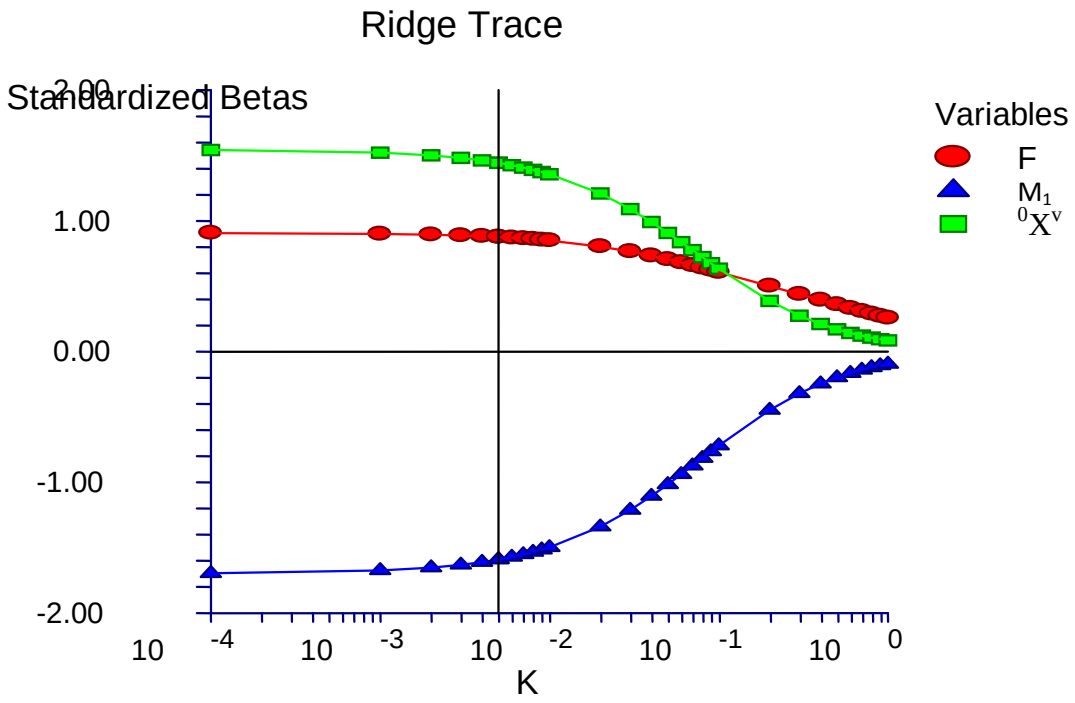

Fig. 3 Ridge Trace Section

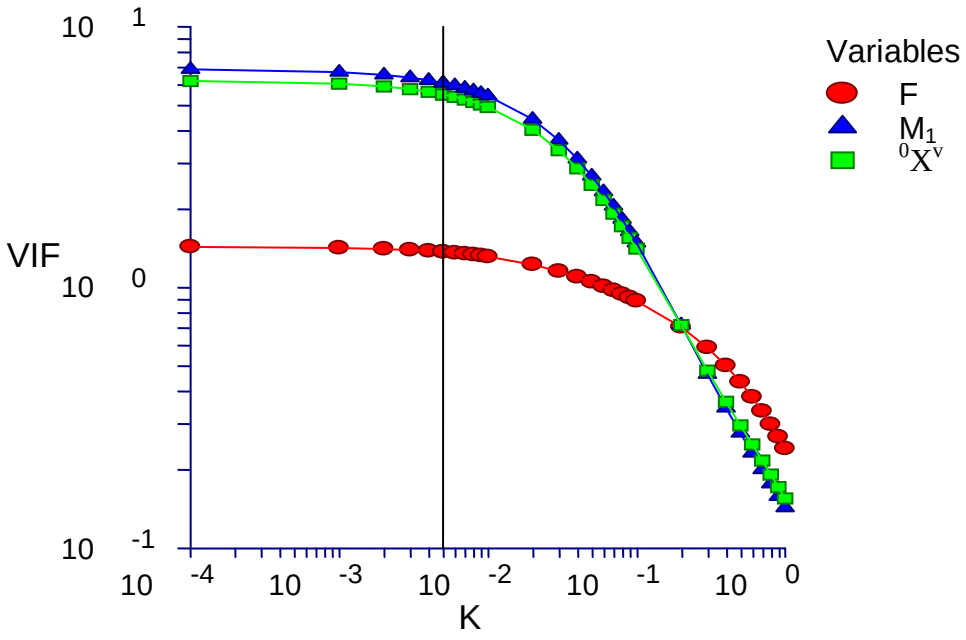

Fig. 4 Variance Inflation Factor Plot

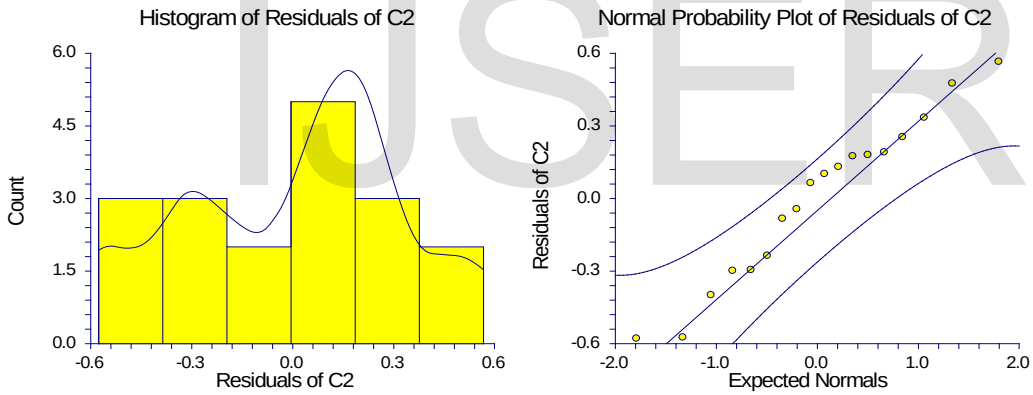

Fig. 5 Residual Plot Section (a) & (b)

3. Experimental Section:

3.1 The Cardiotonic Activity:

The Cardiotonic activity of the series of compounds is taken from the work of Khadikar et al.

3.2 Topological descriptors:

The structure of compounds is drawn by using ACD-labs Chem-sketch Software[39]. The various topological descriptors used in the present study were calculated from the Hydrogen Suppressed molecular graphs of Isoniazide derivatives by using Dragon software[40].

3.3 Regression Analysis:

The correlation-regression analysis of the data was done by using NCSS-8 software[41] as well as Origin-6 software.

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5. Conclusion:

The aforementioned results and discussion lead us to conclude that in topological modeling of Cardiotonic Activity, Balaban Index F, Zagreb's Index M_1 and Kier & Hall's Zero-order Valency Connectivity Indicex ${}^0\chi^v$ play a dominating role and yield excellent tri-parametric model.

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