Available online at http://www.journalcra.com

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

International Journal of Current Research
Vol. 13, Issue, 04, pp.16837-16843, April, 2021

ISSN: 0975-833X

DOI: https://doi.org/10.24941/ijcr.41131.04.2021

RESEARCH ARTICLE **OPEN ACCESS**

QSAR MODELING OF SYNTHETIC ANTIOXIDANT CHROMONE DERIVATIVES USING PHYSICOCHEMICAL AND TOPOLOGICAL PARAMETERS

Dr. Renu Kumari[1*], Dr. Sushil Kumar[2], Dr. Manish Rao Ambedkar[3] and Dr. Madhu gupta[4]

Department of Chemistry D.B.S (PG) College, CSJM University, Kanpur, Uttar Pradesh, India.[1]
S. K. D. G. D. M. K. Post Graduate College, Sardarsahar, Rajasthan[3]
Maharaja Ganga Singh University Bikaner Rajasthan India[3]
MMH PG College, Ghaziabad, India[1,2,3,4]
Chaudhary Charan Singh University Meerut[1,2,3,4]

ARTICLE INFO

Article History:
Received 15th January, 2021
Received in revised form
14th February, 2021
Accepted 19th March, 2021
Published online 24th April, 2021

Key Words:

QSAR, Topological Indices,
Regression Analysis,
Antioxidants,
Physicochemical Parameters.

ABSTRACT

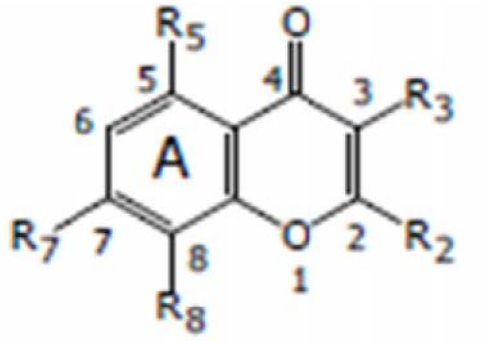
The study presents quantitative structure activity relationships (QSAR) study on A series of 7-hydroxy, 8-hydroxy and 7,8-dihydroxy synthetic chromone derivatives for their DPPH free radical scavenging activities. A training set of 36 synthetic chromone derivatives was subject to two-dimensional quantitative structure-activity relationship (2D-QSAR) studies using leave one out method(Loo method). Regression analysis was carried out using multiple regression analysis. A highly predictive and statistically significant model was generated. The modeling was done using physicochemical and topological parameters. The results are discussed on various statistical parameters. The predictive powers of the models were also discussed by using the method of cross-validation.Our best seven parameteric model having n=36,S.E=0.1767,R^2=0.8637,R^2A=0.8296,F-ratio=25.350,Q=5.2595. Our results shows that the model suggested by us using 2D QSAR technology is comparatively better than the result obtained by Weerasak Samee et. al. used 3D QSAR technique. Hence MLR method is better in the case when connectivity and information indices along with indicator and topological parameter are used as correlating parameters.

Citation: Dr. Renu Kumari, Dr. Sushil Kumar, Dr. Manish Rao Ambedkar and Dr. Madhu Gupta. *"*QSAR modeling of synthetic antioxidant chromone Derivatives using physicochemical and topological parameters*", 2021. International Journal of Current Research, 13, (04), 16837-16843.*

INTRODUCTION

Antioxidant means "against oxidation." An antioxidant is any substance that retards or prevents deterioration, damage or destruction by oxidation (1). Free radicals are formed continuously as normal by-products of oxygen metabolism during mitochondrial oxidative phosphorylation. Thus the mitochondrion is the main source of free radicals (3, 4). The role of free radicals in many disease conditions has been well established. Several biochemical reactions in our body generate reactive oxygen species and these are capable of damaging crucial bio-molecules. If they are not effectively scavenged by cellular constituents, they lead to disease conditions (5, 6) e.g. Cerebrovascular Disease, Cancer, Arteriosclerosis, Atherosclerosis, Heart Disease, Senility, Aging, Behcet's Disease, Crohn's Disease, Cataracts, Sunburn, Ulcers, Osteoporosis,Rheumatoid Arthritis, Diabetes Mellitus, Emphysema, Stroke (2), Rheumatoid Arthritis, Hemorrhagic Shock, Cardiovascular Disorders, Cystic Fibrosis, Neurodegenerative Diseases (e.g. Parkinsonism, Alzheimer's disease), Gastrointestinal Ulcerogenesis, AIDS and even early Senescence (5, 6). Free radicals also spoil foods and degrade materials such as rubber, gasoline and lubricating oils (7). Among the computional method the, QSAR relationships have found diverse application for predicting the compound properties, including biological activity prediction, and toxicity predictions (8-10).

Corresponding author:** ***Dr. Renu Kumari,
Department of Chemistry D.B.S (PG) College, CSJM university, kanpur, Uttar pradesh, India.



The studies on QSAR for relating the chemical or biological activity of drugs or aromatic compounds has led to proliferation of methods and indices (11-13). Such methods include various forms of univariate or multivariate regressions .At a fundamental level, indices include various forms of pure graph invariants commonly called topological indices. Such as Balaban(J), Randic ($^{m}\chi$), Kier and Hall ($^{m}\chi^{v}$) indices. There have been a large number of other less fundamental indices, which have attempted to capture the essence of molecular shape, reactivity and polarity. Such indices are successfully used in modeling of biological activity of organic compounds toxic to the external environment. A series of papers have been published using physicochemical parameters and topological descriptors simultaneously for successful modeling of biological activities for various drug molecules (14-19).

RESULTS AND DISCUSSION

The set of 36 chromone derivative have been used and logEC_{50} activity along with different substituents are recorded in table-1.The table -1 also records the value of indicator parameter namely IP1. IP1 has been taken as unity for the presence of halogen in the compound otherwise its value is zero. The calculated value of topological and physicochemical parameters along with different connectivity and information indices are recorded in table-2.The correlation between the topological indices and their correlation with other parameters are presented in table-3.

Table 1. Molecular structures and corresponding antioxidant activities of synthetic chromones

Cmpd no	R_2	R_3	R_5	R_7	R_8	logEC_{50}	IP1
1.	Phenyl	H	H	OH	OH	1.983	0
2.	Phenyl	H	H	OH	H	2.099	0
3.	Benzyl	H	H	OH	H	2.097	0
4.	4’-(NO_2)-phenyl	H	H	OH	H	2.008	0
5.	3’-(CF_3)-phenyl	H	H	OH	H	1.970	1
6.	4’-(F)-phenyl	H	H	OH	H	2.054	1
7.	3’,5’-(diNO_2)-phenyl	H	H	OH	H	1.942	0
8.	3’-(Cl)-phenyl	H	H	OH	H	2.068	1
9.	4’-(t-butyl)-phenyl	H	H	OH	H	2.019	0
10.	phenyl	CH_3	H	OH	H	2.094	0
11.	Benzyl	CH_3	H	OH	H	2.092	0
12.	4’-(NO_2)-phenyl	4’’-(NO_2)-Benzoyl	H	OH	H	1.773	0
13.	4’-(CF_3)-phenyl	3’’-(CF_3)-Benzoyl	H	OH	H	1.735	1
14.	4’-(F)-phenyl	4’’-(F)-Benzoyl	H	OH	H	1.860	1
15.	3’,4’-(diF)-phenyl	3’’,4’’-(diF)-Benzoyl	H	OH	H	1.799	1
16.	4’-(OCH_3)-phenyl	4’’-(OCH_3)-Benzoyl	H	OH	H	1.850	0
17.	3’-(CF_3)-phenyl	H	OH	OH	H	1.932	1
18.	4’-(F)-phenyl	H	OH	OH	H	2.010	1
19.	3’,4’-(diF)-phenyl	H	OH	OH	H	1.994	1
20.	4’-(t-butyl)-phenyl	H	OH	OH	H	1.941	0
21.	3’-(Cl)-phenyl	H	OH	OH	H	2.018	1
22.	3’,4’-(diCl)-phenyl	H	OH	OH	H	1.955	1
23.	4’-(OCH_3)-phenyl	H	OH	OH	H	2.039	0
24.	3’-(OCH_3)-phenyl	H	OH	OH	H	2.048	0
25.	3’,4’-(diNO_2)-phenyl	H	OH	OH	H	1.902	0
26.	4’-(NO_2)-phenyl	4’’-(NO_2)-Benzoyl	OH	OH	H	1.756	0
27.	phenyl	H	H	OH	OH	1.504	0
28.	Benzyl	H	H	OH	OH	1.581	0
29.	3’-(CF_3)-phenyl	4’’-(CF_3)-Benzoyl	H	OH	OH	0.417	1
30.	4’-(F)-phenyl	4’’-(F)-Benzoyl	H	OH	OH	0.594	1
31.	CH_3	H	H	OH	H	2.262	0
32.	3’,4’-(diCl)-phenyl	H	H	OH	H	2.001	1
33.	4’-(NO_2)-phenyl	H	H	OH	H	1.956	0
34.	CH_3	H	H	OH	OH	1.616	0
35.	3’-(OCH_3)-phenyl	3’’-(OCH_3)-Benzoyl	H	OH	H	1.847	0
36.	4’-(NO_2)-phenyl	4’’-(NO_2)-Benzoyl	H	OH	OH	0.528	0

Ip1=1if halogens present in compounds, otherwise zero.

Table 2. Values of Topological, Randic connectivity indices and Information indices used for the compounds used in the present study

Compd no	J	$^{1}\chi$	$^{2}\chi$	$^{3}\chi$	SIC1	MLOGP
1.	1.67	8.754	7.843	6.775	0.58	2.581
2.	1.638	8.737	7.494	6.631	0.58	2.581
3.	1.551	9.22	8.397	6.767	0.632	2.562
4.	1.571	10.042	9.47	7.74	0.663	2.579
5.	1.645	10.342	10.541	7.921	0.659	3.461
6.	1.615	9.131	8.571	7.042	0.646	2.974
7.	1.695	11.346	11.026	8.683	0.68	2.431
8.	1.642	9.131	8.583	6.958	0.646	3.098
9.	1.573	10.342	10.529	7.978	0.62	3.543
10.	1.709	9.165	8.358	7.314	0.63	2.83
11.	1.620	9.648	8.796	7.518	0.644	2.805
12.	1.498	15.257	14.375	12.13	0.588	3.038
13.	1.613	16.269	17.066	12.799	0.604	4.142
14.	1.539	13.436	12.577	10.732	0.573	3.594
15.	1.566	14.257	13.593	11.889	0.606	3.805
16.	1.509	14.512	12.915	11.549	0.581	2.246
17.	1.672	10.753	11.09	8.224	0.683	3.164
18.	1.65	9.542	9.12	7.345	0.674	2.677
19.	1.666	9.952	9.628	7.923	0.703	2.801
20.	1.601	10.753	11.078	8.281	0.639	3.514
21.	1.676	9.542	9.132	7.261	0.674	2.801
22.	1.666	9.952	9.628	7.923	0.703	3.044
23.	1.617	10.08	9.289	7.753	0.676	2.013
24.	1.66	10.08	9.301	7.685	0.676	2.013
25.	1.718	11.757	11.575	8.987	0.7	2.211
26.	1.528	15.668	14.924	12.439	0.612	2.826
27.	1.69	9.165	8.348	7.375	0.614	2.041
28.	1.601	9.648	8.796	7.511	0.66	2.022
29.	1.612	16.286	16.916	13.235	0.604	3.631
30.	1.566	13.863	12.977	11.477	0.6	2.807
31.	2.02	6.165	5.896	4.514	0.788	1.188
32.	1.634	9.542	9.079	7.62	0.679	3.341
33.	1.571	10.042	9.47	7.74	0.663	2.579
34.	2.106	6.592	6.295	5.258	0.793	0.649
35.	1.562	14.512	12.939	11.413	0.581	2.246
36.	1.527	15.684	14.774	12.874	0.612	2.315

list of abbreviations and symbols used:
$^{1}\chi$,$^{2}\chi$, 3χ, = Randic connectivity indices
J= Balaban index
SIC1=information index
MlogP=Lipophicity parameter

Table 3. Correlation matrix

	logEc50	J	1χ	2χ	3χ	SIC1	MLOGP	IP1
logEc50	1.0000							
J	0.1841	1.0000						
1χ	-0.5779	-0.6316	1.0000					
2χ	-0.5811	-0.5696	0.9808	1.0000				
3χ	-0.6184	-0.6135	0.9958	0.9737	1.0000			
SIC1	0.2862	0.7956	-0.6312	-0.5518	-0.6274	1.0000		
MLOGP	-0.0596	-0.6064	0.4719	0.5449	0.4642	-0.5312	1.0000	
IP1	-0.1355	-0.0875	0.1451	0.2220	0.1648	0.0067	0.5885	1.0000

Statistical analysis: In modeling $\log EC_{50}$ for the 36 set of chromone derivative and to arrive at most significant model we have chosen stepwise regression analysis and used maximum R^2 method. Among the proposed model, the best mono to multiparameteric models were found to be the following.

One-parametric model: It was observed that among the several monoparametric model, the model containing 3χ (third order connectivity index)was found to be the best with R^2=0.3825 is as follows:

$$\log EC_{50=}2.8229-0.1158(\pm0.0252)\ 3\chi \quad (1)$$

n=36, S.E=0.3414, R^2=0.3825, R^2A =0.3643, F-ratio=21.060, Q=1.8115

In the above eqn. n= no of compounds, S.E= Standard error of estimation, R^2= coefficient of determination, R^2A = adjusted R^2 ,Q= Quality factor. In the above model the negative value of 3χ indicates that decrease in the value of this the biological activity can be enhanced.

Two-parametric model: Among the several biparameteric model when the 1χ(first order connectivity index) was combined with the 3χ parameter the R^2 value increased significantly from 0.3825 to 0.5564.The quality factor also enhances from the value of 1.8115 to 2.5397.The model is as given below:

$logEC_{50}$ =2.1817+0.7283(±0.2025) 3χ -0.9701(±0.2385) 1χ
n=36, S.E=0.2937, R^2=0.5564, R^2A =0.5295, F-ratio=20.697, Q=2.5397 (2)

Three-parametric model: In the tri parametric model when another second order connectivity parameter (2χ) wasCombined with the above biparameteric model containing 3χ and 1χ.The significant improvement in the value of R^2 was observed .The R^2 value increases from the value of 0.5564 to 0.5809 and the quality factor enhance from 2.5697 to 2.6290.The value of S.E. was decreased from 0.2397 to 0.0.2899.The model is as shown below.

$logEC_{50}$= 2.0752+0.9025(±0.2371) 1χ -0.1267(±0.0928) 2χ-1.0261(±0.2389) 3χ
n=36, S.E=0.2899, R^2=0.5809, R^2A =0.5416, F-ratio=14.783, Q=2.6290 (3)

Four-parametric model: Among the four parameteric model ,the model containing 1χ , 2χ, 3χ along with MLOGP was found to be the best. The model is as given below.

$logEC_{50}$ =1.6530+1.0173(±0.2125)1χ -0.2660(±0.0930)2χ-1.0334(±0.2110)3χ + 0.2514 (±0.0794) MLOGP

n=36, S.E=0.2560, R^2=0.6834, R^2A =0.6425, F-ratio=16.725, Q=3.2292 (4)

In the model given above the inclusion of MLOGP drastically increases the value R^2 from 0.5809 to 0.6834.

Five-parametric model: When to the above four parameteric model another topological parameter J (Balaban index) have been found to be effective with R^2=0.7529.The model is as below.

$logEC_{50}$= -3.1685+2.1246(±0.7310)J+.5587(±0.2666)1χ-0.5444(±0.1271)2χ-1.3099(±0.2120)3χ + 0.5027(±0.1121) MLOGP
n=36, S.E=0.2299, R^2=0.7529, R^2A =0.7118, F-ratio=18.285, Q=3.7742. (5)

Six-parametric model: However in case of six parametric modeling a model containing J,1χ,2χ ,3χ, SIC1 ,MLOGPcomes out to be the best. The R^2value for this model is 0.8170.The model is as below:

$logEC_{50}$=-6.3624+1.8512(±0.6456)J+ 1.8510(±0.2508) 1χ-0.7699(±0.1318) 2χ-1.3601(±0.1863) 3χ+ 4.2678(±1.3400)SIC1 +0.6718(±0.1115)MLOGP
n=36, S.E=0.2012., R^2=0.8170, R^2A =0.7791, F-ratio=21.572, Q=4.4924 (6)

Seven-parametric model: The best seven parametric model containing indicator parameter IP1 taken for the presence of halogen group in the given compounds is as follows.

$logEC_{50}$= -8.6415+2.2062(±0.5784)J+1.8443(±0.2203)1χ -0.8611(±0.1195) 2χ-1.2334(±0.1686) 3χ +5.9580(±1.2970) SIC1-0.2933(±.0946) IP1 n=36, S.E=0.1767, R^2=0.8637, R^2A =0.8296, F-ratio=25.350, Q=5.2595 (7)

However, seven parametric model with J, 1χ, ^{2}χ, 3χ,SIC1, IP1 comes out to be the best since it gives a highest R^2 and Q value(21). Using model 7 (table-4) the $logEC_{50}$ values have been evaluated and reported in table-5 respectively.

Table 4. Regression parameters and quality of correlation for the various models

Model. No	Paramet-ers used	Ai = (1----7)	B	Se	R^2	R^2A	F-ratio	Q = R/Se
1	3χ	-0.1158(±0.0252)	2.8229	0.3414	0.3825	0.3643	21.060	1.8115
2	3χ 1χ	0.7283(±0.2025) -0.9701(±0.2385)	2.1817	0.2937	0.5564	0.5295	20.697	2.5397
3	1χ 2χ 3χ	0.9025(±0.2371) -0.1267(±0.0928) -1.0261(±0.2389)	2.0752	0.2899	0.5809	0.5416	14.783	2.6290
4	1χ 2χ 3χ MLOGP	1.0173(±0.2125) -0.2660(±0.0930) -1.0334(±0.2110) 0.2514(±0.0794)	1.6530	0.2560	0.6834	0.6425	16.725	3.2292
5	J 1χ 2χ 3χ MLOGP	2.1246(±0.7310) 1.5587(±0.2666) -0.5444(±0.1271) -1.3099(±0.2120) 0.5027(±0.1121)	-3.1685	0.2299	0.7529	0.7118	18.285	3.7742
6	J 1χ 2χ 3χ SIC1 MLOGP	1.8512(±0.6456) 1.8510(±0.2508) -0.7699(±0.1318) -1.3601(±0.1863) 4.2678(±1.3400) 0.6718(±0.1115)	-6.3624	0.2012	0.8170	0.7791	21.572	4.4924
7	J 1χ 2χ 3χ SIC1 MLOGP IP1	2.2062(±0.5784) 1.8443(±0.2203) -0.8611(±0.1195) -1.2334(±0.1686) 5.9580(±1.2970) 0.9121(±0.1249) -0.2933(±.0946)	-8.6415	0.1767	0.8637	0.8296	25.350	5.2595

However, the correlation potential for these model have obtained by plotting observed versus estimated $logEC_{50}$values and they are demonstrated in Fig-1 and predictive power of the Fig-1 comes out to be 0.8637 suggesting that this model is the best among all the models. The model-7explains more than 86 % variance of the data. Further confirmation in favour of seven parametric model is obtained by calculating the cross-validated parameters (table-6) for the given models. PRESS (predicted residual sum of squares) appears to be the most important cross validation parameter accounting for a good estimate of the real predictive error of the models. Its value less than SSY (sum of squares of the response value) indicate that the model predict better than the chance and can be considered statistically significant. In our case PRESS/SSY for all the models has been more than zero, which shows that these models are free from the defect of chance and also R^2Cv is highest for the seven parametric models suggesting that this model is most appropriate for modeling $logEC_{50}$ value of compounds under investigation.

Table 5. Observed and estimated logEC50 values using modelno. 7.

Compd no	Observed $logEC_{50}$	Predicted $logEC_{50}$	Residual
1	1.983	1.888	0.095
2	2.099	2.264	-0.165
3	2.097	2.31	-0.213
4	2.008	1.946	0.062
5	1.97	2.004	-0.034
6	2.054	1.964	0.09
7	1.942	2.088	-0.146
8	2.068	2.23	-0.162
9	2.019	1.921	0.098
10	2.094	2.148	-0.054
11	2.092	2.275	-0.183
12	1.773	1.736	0.037
13	1.735	1.523	0.212
14	1.86	1.865	-0.005
15	1.799	1.526	0.273
16	1.85	1.596	0.254
17	1.932	1.848	0.084
18	2.01	1.848	0.162
19	1.994	1.775	0.219
20	1.941	1.981	-0.04
21	2.018	2.112	-0.094
22	1.955	1.997	-0.042
23	2.039	1.819	0.22
24	2.048	1.987	0.061
25	1.902	1.967	-0.065
26	1.756	1.656	0.100
27	1.504	1.225	0.279
28	1.581	1.622	-0.041
29	0.417	0.677	-0.26
30	0.594	0.892	-0.298
31	2.262	2.319	-0.057
32	2.001	2.145	-0.144
33	1.956	1.946	0.01
34	1.616	1.573	0.043
35	1.847	1.86	-0.013
36	0.528	0.81	-0.282

Table 6. Cross-validated parameters

Model no.	Parameters used	PRESS	SSY	PRESS /SSY	R^2_{CV}	PSE	S_{PRESS}
2.	3χ 1χ	2.8472	3.5715	0.7972	0.2028	0.2812	0.2935
3.	1χ 2χ 3χ	2.6903	3.7284	0.7215	0.2785	0.2733	0.2899
4.	1χ 2χ 3χ MLOGP	2.0324	4.3862	0.4633	0.5367	0.2376	0.2560
5	J 1χ 2χ 3χ MLOGP	1.5858	4.8328	0.3281	0.6719	0.2098	0.2299
6	J 1χ 2χ 3χ SIC1 MLOGP	1.1749	5.2438	0.2241	0.7759	0.1806	0.2012
7	J 1χ 2χ 3χ SIC1 MLOGP IP1	0.8747	5.5439	0.1577	0.8423	0.1558	0.1767

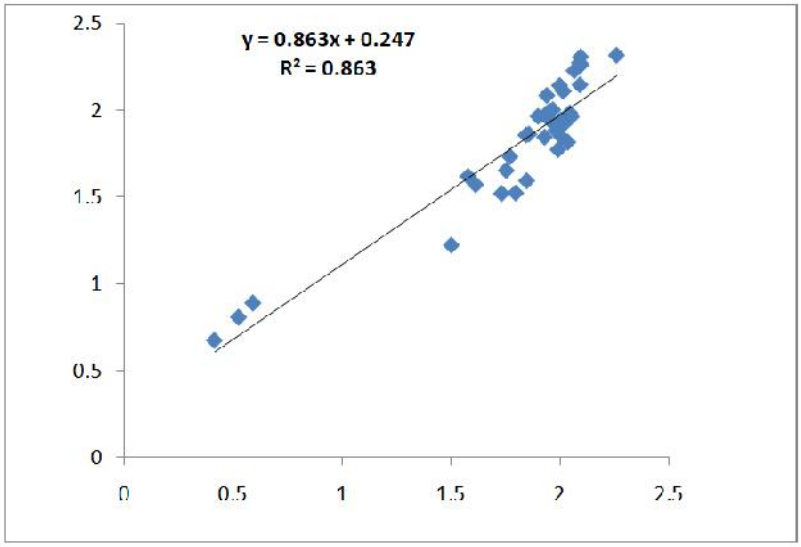


Fig 2. Correlation between observed and estimated logEC_{50} using model no.7

Experimental

50% Effective concentration (log* EC_{50}*) Activity: The biological activity studied here is the 50% Effectiveconcentration (log EC_{50}) of36 synthetic antioxidant chromone derivatives as reported earlier is used.

Molecular descriptors used: The molecular structures of chromone derivatives were modeled with chemsketch software and also several physicochemical parameters for the 36 synthetic antioxidant chromone derivatives were calculated using ACD Lab software chem sketch (20). Topological indices for the 36 antioxidant chromone derivatives have been calculated using Dragon software. They are Balaban, Ranadic connectivity and information indices. They are reported in table-2 respectively. All the topological indices were calculated from the hydrogen suppressed graphs. These graphs were obtained after deleting all the carbon-hydrogen as well as heteroatoms -hydrogen bonds from the molecular structures of the compound used . The structure optimization for using Dragon software was made by ACD Lab's software.

Regression analysis: Regression analysis was made using maximum R^2 method following stepwise regression analysis. The NCSS software was used for making regression analysis.

Conclusion

The above result suggests the following conclusion.

- Second and third order connectivity indices have retarding role towards logEC_{50} activity.
- 1χ , MLOGP and SICI(Information index) supports the biological activity i.e. logEC_{50} .
- Increase in the value of J (Balaban index) enhances the activity.
- The presence of halogen group indicated that halogen group on ring A alsoretards logEC_{50} activity.
- Our results shows that the model suggested by us using 2D QSAR technology is comparatively better than the result obtained byWeerasak Samee et. al.(22) used 3D QSAR technique. Hence MLR method is better in the case when connectivity and information indices along with indicator and topological parameter are used as correlating parameters.

Acknowledgement

Authors are thankful to the referees for their valuable suggestions making the paper in this form .I am also thankful to professor V.K. Agrawal Director, NITTTR, Bhopal for their generous help and encouragement for presenting this work. I am also thankful to U.G.C New Delhi for giving us a financial support.

REFERENCES

1 Dekkers, J.C., L.J.P. Doornen and C.G. Han,. The Role of Antioxidant Vitamins and Enzymes in the Prevention of Exercise-Induced Muscle Damage. *Sports Med*., 21, 213-238,1996.
2 Sharma, H. and C. Clark,. An excerpt from the medical textbook Contemporary Ayurved., Edinburgh: Churchill Livingstone, ISBN: 0 443055947,1998.
3 Przedborski, S. and V. Jackson-Lewwis,. Experimental developments in movements disorders: update on proposed free radical mechanisms. *Current Opinion Neurol.*, 11,1998,335-339.

4 Fahn, S. and G. Cohen,. The oxidative stress hypothesis in Parkinson's disease: Evidence supporting it. *Ann. Neurol.,* 32,1992, 804-812.
5 Halliwell, H,. Free radicals, antioxidants and human disease: Curiosity, cause or consequence? Lancet. 344,1996, 721-724,.
6 Halliwell, B. and J.M.C. Gutteridge,. In: Free radicals, ageing and disease, Free radicals in Biology and Medicine. Clarendron Press, Oxford. 2,1985, 279-315.
7 Dexter, D.T., J. Sian and S. Rose,. Indices of oxidative stress and mitochondrial function in individuals with incidental Lewy body disease. *Ann. Neurol.*, 53,1994,38-44.
6 Eldred, D.V., Weikel, C.L., Jurs, P.C., Kaiser, K.L.E., Prediction of fathead minnow acute toxicity of organic compounds from molecular structure. *Chem. Res. Toxicol.* 12,1999,670–678.
7 Kauffman, G.W., Jurs, P.C.,. Prediction of the sodium ion-proton antiporter by benzoylguanidine derivatives from molecular structure. *J. Chem. Inf. Comput. Sci.* 40, 2000,753–761.
8 Patankar, S.J., Jurs, P.C.,. Prediction of IC50 values for ACAT inhibitors from molecular structure. *J. Chem. Inf. Comput. Sci*. 40,2000, 706–723.
9 Wessel, M.D., Jurs, P.C., Tolan, J.W., Muskal, S.M.,. Prediction of human intestinal absorption of drug compounds from molecular structure. *J. Chem. Inf. Comput. Sci*. 38, 1998,726–735.
10 DeWeese, A.D., Schultz, T.W., Structure–activity relationships for aquatic toxicity to tetrahymena: halogen substituted aliphatic esters. *Environ. Toxicol.* 16, 2001, 54–60.
11 H.Wiener., *J.Am.Chem .Soc*.,69 ,1947,17-20.
12 M.Randic., *J.Am.Chem.Soc*.,97,1975,6609-6615.
13 L.B. Kier, L, H Hall Molecular connectivity in structure activity Relationship; Wiley, New york.1986, L.B .Kier, L.H Hall molecular structure Description, Academic press, New York, 1999.
14 Agrawal V.K., Singh J., Pandey A., Khadikar P.V., Modeling of inhibitory Activities of sulfanilamide Schiff bases using Physicochemical properties,*Oxidation commun*., 29(4),2006,803-816.
15 Agrawal V.K., Singh J.,Karmarkar S., Khadikar P.V., QSAR Studies on some anti-HIV-1 Drugs: Deoxy Analogues of Hept-1, *Oxidation commun*.1,2008,27-43.
16 Agrawal V.K., Singh J.,Louis Bruno., Khadikar P.V., The topology of Molecules and its Lipophilicity,*Current Computer - Aided Drug Design*, (CCADD), 2,2006, 369-403.
17 Singh J., Singh S.,Shaik B., Sohani N.,Agrawal V.K., Khadikar P.V.,Mutagenicity of Nitrated polycyclic Aromatic Hydrocarbons: A QSAR Investigation Chemical Biology Drug Design-71,2008,230-243.
18 Singh J.,Ahamad I., Shaik B.,Kumar R.,Gupta M ., Agrawal V.K.,Modeling of Protease Inhibitory Activity Of Some Hydroxymates using Physicochemical and Topological Parameters, *International Journal of Pure & Applied Chemistry* 4(3),2009,195-203.
19 Kumari R.,Kumar S.,Amita,Gupta M., Quantitative structure activity relationship using MLR method for nitrobenzenes toxicity to *tetrahymena pyriformis.*, *International Journal ofsyntheses and Characterization.*,3(2),2010,77-85.
20 Chem Sketch: *www.acdlabs.com.*
21 Pogliani L., from Molecular Connectivity Indices to Semi imperical Connectivity Terms: Recent trends in graph theoretical Descriptors, *Chem.Rev*.100,2000, 3827-3858.
22 Weerasak Samee, Patcharawee Nunthanavanit and Jiraporn Ungwitayatorn .,3D-QSAR Investigation of Synthetic Antioxidant Chromone Derivatives by Molecular Field Analysis.,*Int. J. Mol. Sci*. 9,2008, 235-246.

****