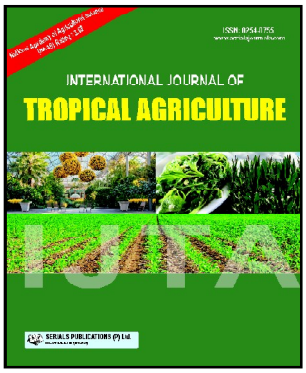

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Effect of Topological Indices on Antimalarial Activities of Flavin Derivatives

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Abstract: Flavin derivatives have been found, to behave as anti malarial agents. In the present investigation, QSAR analysis for the seventeen flavin derivatives along with their activity; Log ED_{40}. (effective dose that produces a therapeutic response in 40% of the people taking it) was carried out using physico-chemical as well as topological parameters. The basis of the current investigation, has to model the activity (i.e. Log ED_{40}, in the present study.) Two indicator parameters (IP) have also been taken. A stepwise regression analysis followed by statistical evaluation of the data revealed the influence of topological and indicator parameters are the best to model the activity. The model obtained has superior statistic in terms of R^2 value of 0.9404, Q value of 7.094 and Se = 0.1495. Hence the best model obtained showed that the second order valence connectivity index ($^2\chi^v$) has retarding role towards activity (log ED_{40}) and third order valence connectivity index ($^3\chi^v$) has a positive role towards the activity. Presence of halogen atom at meta and para position should be avoided. The model obtained had also the best cross validated parameters like; PRESS, SSY, R^2_{CV}, S_{PRESS} and PSE.

Key words: QSAR, regression analysis, indicator parameters, cross validation.

1. INTRODUCTION

Malaria remains one of the most severe infectious diseases in the world. It leads to more than 300 million new clinical cases and about.7 million deaths each year, mostly among children. About half of the world population, particularly that of underdeveloped countries, is at high risk for malaria infection.

Malaria is caused by unicellular eukaryotic parasites of the genus Plasmodium. Of the five types

of Plasmodium parasites that can infect humans, *Plasmodium falciparum* is the most lethal strain. Because of drug resistance, certain prophylactic and therapeutic drugs, such as chloroquine, have lost or are losing their clinical effectiveness. Therefore, novel effective antimalarial compounds continue to be in high demand. Flavin derivatives are one of the potent anti malarial agents currently in use.

The present study is carried out to establish the relationship between the structural aspects of flavin derivatives and its anti malarial activity through QSAR analysis using a mixture of physiochemical and topological indices. The basic structure of flavin is depicted below:

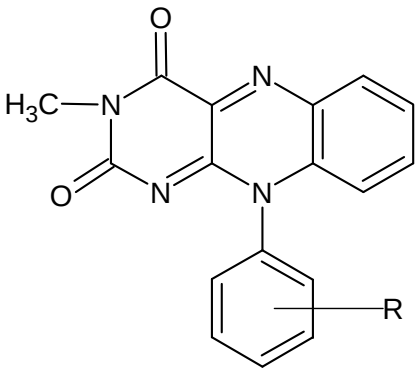

Figure 1: Basic structure of flavin derivative

The activity used in the present study is Log ED_{40}. (effective dose that produces a therapeutic response in 40% of the people taking it) reported by Jefford et al **[1]** and Posner *et al.* **[2]** and **Table-1**, presents the structural details of the 17, 3-methyl–10 (substituted- phenyl) flavins, along with their activity, log ED_{40} . Two indicator parameters have also been taken, IP_1 which accounts, when "R" is mono substituted with halogen at meta position and IP_2 which accounts for the presence of halogen at para position.

2. METHODOLOGY USED

The physiochemical data of the molecules was obtained through the advanced version of Chemsketch software (ACD Labs) **[3]** whereas the topological indices were obtained through Dragon software **[4].** Out of large pool of topological indices present, only valence connectivity indices of zero, first, second and third order **[5,6]** were selected for the present study. The entire data (physiochemical and topological) obtained through various software's for each molecule in the present investigation were statistically analyzed by using latest version of NCSS software **[7]** (specifically used for statistically analysis). Multiple linear regression (MLR) analysis was done in step wise manner to obtain the best model. A large number of equations containing mono, bi , tri and tetra parameters were obtained individually for physiochemical parameters, topological indices and when both were mixed.

Table 1
Structural Details of the compounds with their activity used in the present study along with the value of indicator parameters

Compd. No.	R	*Log* ED_{40}	IP_1	IP_2
1	4-Br	1.5843	0	1
2	4-Cl	1.5888	0	1
3	3,5-di-Cl	1.6042	0	0
4	3-CF_3	1.8992	0	0
5	3-Cl,5-Me	1.9329	1	0
6	4-F	2.0128	0	1
7	3,5-di-Me	2.0211	0	0
8	4-CF_3	2.1303	0	0
9	4-OMe	2.1398	0	0
10	3-Br	2.1702	1	0
11	4-Cl,3-Me	2.2600	0	1
12	3,4-di-Me	2.3222	0	0
13	3,5-di-OMe	2.3404	0	0
14	3-Cl	2.3598	1	0
15	H	2.3944	0	0
16	4-Et	2.4487	0	0
17	3-Cl,4-Me	2.6589	1	0

IP_1 = 1, if R is mono substituted with halogen at third position;

IP_2 = 1, if halogen is present at fourth position.

However, the combination of topological indices along with the indicator parameters gave superior results in terms of statistics. The result obtained through this method is presented in terms of R^2, R^2_A, F ratio, Se and Q value **[8,9,10]** (the details of these parameters can be found in the standard statistical books).

The statistical data obtained through the above analysis was further evaluated through cross validation, reported in **Table 2.**

The results obtained through cross validation confirmed the superiority of the model obtained.

Table 2
Cross Validated Parameters

Parameters Used	*PRESS*	*SSY*	*PRESS/SSY*	R^2_{CV}	S_{PRESS}	*PSE*
$^2\chi^v$, $^3\chi^v$, IP_1 IP_2	0.2682	1.3131	0.2042	0.7958	0.1494	0.1256

3. RESULTS AND DISCUSSION

A large number of regression models obtained **[11]**, were comparatively analyzed in terms of their statistical output. A thorough verification of the data revealed the fact that the physiochemical parameters either alone or in combination with topological parameters were not found to be suitable to model the activity. Hence, they were discarded from the further study.

However, the regression models obtained by using only topological parameters, found to be better than the physiochemical indices. Henceforth the further investigation was concentrated on topological indices only. The topological indices along with the combination of indicator parameters (discussed earlier), were found to be the suitable to model the activity.

The multiple linear regression analysis, of the data obtained signifies the importance of topological indices and indicator parameters in modeling the activity of the compounds. Although a large number of mono, bi and tri parametric models were found to be statistically significant but as the rule of thumb, we have selected and analyzed only tetra parametric models. Among a large number of tetra parametric models, the model finally selected is presented below:

$$\text{Log } ED_{40} = -1.3010(\pm 0.2038)\ ^2\chi^v + 1.7571(\pm 0.2974)\ ^3\chi^v - 0.2941(\pm 0.0949)\ IP_1 - 0.2915(\pm 0.0899)\ IP_2 + 2.3766$$

$N = 17$, $Se = 0.1495$, $R^2 = 0.8304$, $R^2_A = 0.7738$, F-Ratio $= 14.686$, $Q = 6.0954$

The above presented model was further cross validated by the help of cross validated parameters.

4. CONCLUSION

Hence, keeping in view the above model and the cross validation results, following facts must be kept under consideration to model log ED_{40}:

1) Presence of halogens at meta and para positions, must be avoided.
2) Second order Kier- Hall valence connectivity index should be kept as low as possible while, the third order Kier- Hall valence connectivity index should be increased.

Further confirmation was obtained by plotting the graph between observed and estimated log ED_{40} values **(Table 3)** using the above model. The predictive power of **0.8304**, suggests that about **83%** of the variance in the data could be explained using this model.

Table 3
Comparison of observed and estimated activity (Log ED_{40})

Compd.No.	*Observed Log ED_{40}*	*Estimated Log ED_{40}*	*Residual*
1	1.5840	1.6520	-0.0680
2	1.5880	1.7890	-0.2010
3	1.6040	1.6770	-0.0730
4	1.8990	2.0710	-0.1720
5	1.9320	2.0020	-0.0700
6	2.0120	1.9140	0.0980
7	2.0210	1.7420	0.2790
8	2.1300	2.1130	0.0170
9	2.1390	2.3490	-0.2100
10	2.1700	2.1390	0.0310
11	2.2600	2.0890	0.1710
12	2.3220	2.3420	-0.0200
13	2.3400	2.3280	0.0120
14	2.3590	2.3090	0.0500
15	2.3940	2.2660	0.1280
16	2.4480	2.4080	0.0400
17	2.6580	2.6690	-0.0110

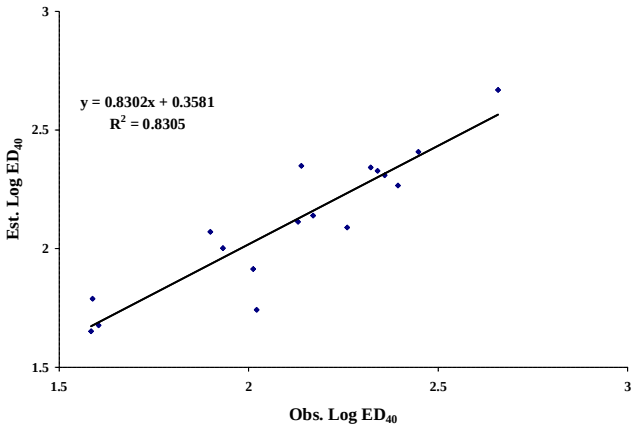

Figure 2: Correlation between observed and estimated activity (Log ED_{40})

The above investigation also reflects the power of QSAR models, to use it as a tool not only for modeling the activity but also to study the various structural aspects of a molecule (like its conformation or presence or absence of suitable groups in a moiety) which is responsible for its increased activity or its sluggish nature towards certain microbial groups.

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