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STUDIES ON ANTIMALARIAL ACTIVITY OF CYCLIC PEROXY CETALS USING NEWLY INTRODUCED BALABAN INDICES

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ABSTRACT

In this paper, we have done the development of new anti-malarial compounds using graph theoretical descriptors as molecular descriptors for the series of peroxy cetals. The resulting QSAR (quantitative structure- activity relationship) helps the pharmaceutical chemistry for the manufacturing of new anti-malarial compounds. Here, we are using newly introduced F and G indices for proposing most significant QSAR model for modeling antimalarial activity of peroxy cetals. Results are discussed on the basis of statistical parameters.

Key words: Antimalarial agent, Regression analysis, Topological index.

INTRODUCTION

Nearly 100 millions (10 crores) of people, all over the world, are attacked by malaria every year of which about 1% (mostly children) die. Malaria is caused by a protozoon, belonging to the sub-phylum of sporozoa and the genus plasmodium. Four species of plasmodium are clinically important: (i) P. vivax (ii) P. falciparum (iii) P. ovale and (iv) P. malariae. Out of them, P. vivax and P. falciparum are important.

Malaria parasites invade RBC causing hemolysis. This is a major cause of anemia due to malaria. Hemolytic jaundice can develop P. falciparum induced hemolysis, which is particularly more severe. In P. falciparum malaria, RBCs containing schizoints cling to the walls of capillaries of vital organs like brain/kidney. This can cause hypoxia of the organ concerned. Further, rupture of these schizoints containing RBCs cause further hypoxia leading to damage of the organ and death may result.

New drugs with still better relief giving potential are synthesized employing the

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application of mathematical concept called graph theory and topology. All such new compounds are possible to prepare employing combinatorial and throughout chemistry. Such new synthesis is possible by the correlation analysis and that correlation is investigated by correlating the activity with topological indices. Needless to state that topological index is a numerical representation of molecular structure. Hence, quantitative structure-activity relationship (QSAR) is only possible using topological indices as molecular descriptors. In the present study, we have attempted QSAR study on the modeling of antimalarial activity of peroxy cetals (Table 1) using stepwise regression analysis.

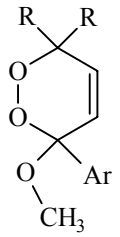

Table 1:

S. No.	Ar	R, R	log (IC_{50})
1	Ph	Me, Me	3.041
2	Ph	Cyclopentyl	2.279
3	Ph	Cyclohexyl	2.447
4	Ph	Cycloheptyl	2.342
5	4-MeOPh	Cyclobutyl	2.204
6	4-MeOPh	Cyclohexyl	2.255
7	4-MeOPh	Cycoheptyl	2.322
8	3,4,5-$(MeO)_3$Ph	Cycloheptyl	2.079
9	4-CF_3	Cycloheptyl	1.785
10	4-ClPh	Cycloheptyl	1.763
11	4-FPh	Cycloheptyl	1.929
12	4-MeSPh	Cycloheptyl	1.892
13	4-$MeS(O)_2$Ph	Cycloheptyl	1.491
14	4-EtPh	Cycloheptyl	2.255

Cont…

S. No.	Ar	R, R	log (IC50)
15	4-MeSPh	Cyclohexyl	2.204
16	4-MeS$(O)_2$Ph	Cyclohexyl	1.748
17	4-O_2NPh	Cyclohexyl	1.663
18	4-ClPh	Cyclohexyl	2
19	4-FPh	Cyclohexyl	2.301
20	4-F_3CPh	Cyclohexyl	2.146

In view of this, we have for the first-time used the new topological indices developed by Balaban-Khadikar-Sufia. These indices (F and G) are the 'Shape' indices and therefore, we can use them for investigating the influence of 'Shape' on antimalarial activity. In addition, we have also used the well- known Balaban J index. This J index is supposed to be most discriminate index known and developed in chemical graph theory.

EXPERIMENTAL

Methodology

Balaban-Khadikar-Sufia has introduced two new Balaban type indices viz F and G using the expression of Balaban J index –

$$J = (E/R + 1) \sum_{\text{all edges}} (di.dj)^{-1/2} \quad ...(1)$$

Where E is the number of edges, di and dj are the distance sums and R is cyclomatic number defined by the following expression –

$$R = E - N + 1 \quad ...(2)$$

Where N is the number vertices (atoms) in the molecular graph.

The two new indices F and G are defined by the following expression.

$$F = E \sum (di.dj)^{-1/2} \quad ...(3)$$

$$= J (R + 1) \quad ...(4)$$

and

$$G = [N^2E/N + R + 1] \sum (di.dj)^{-1/2} \quad ...(5)$$

$$= [N^2F/N + R + 1] \quad ...(6)$$

The value of J, F and G along with the value of log $1/IC_{50}$ are presented in Table 2.

Table 2:

Compd. No.	J	R	F	G	nsk	nbo	Log (IC_{50})
1	2.021	2	6.063	81.6909	16	17	3.041
2	1.663	3	6.652	97.9658	18	20	2.279
3	1.648	3	6.592	103.466	19	21	2.447
4	1.648	3	6.592	109.867	20	22	2.342
5	1.607	3	6.428	100.892	19	21	2.204
6	1.606	3	6.424	113.319	21	23	2.255
7	1.61	3	6.44	119.883	22	24	2.322
8	1.7228	3	6.8912	155.281	26	28	2.079
9	1.56	3	6.24	134.483	25	27	1.785
10	1.634	3	6.536	115.295	21	23	1.763
11	1.634	3	6.536	115.29	21	23	1.929
12	1.61	3	6.44	119.883	22	24	1.892
13	1.604	3	6.416	131.986	24	26	1.891
14	1.61	3	6.44	119.883	22	24	2.255
15	1.606	3	6.424	113.319	21	23	2.204
16	1.6	3	6.4	125.393	23	25	1.748
17	1.547	3	6.388	118.915	22	24	1.663
18	1.632	3	6.536	108.933	20	22	2
19	1.632	3	6.536	108.933	20	22	2.301
20	1.6	3	6.4	125.393	23	25	2.146

The statistical parameters obtained are very useful to investigate the participation of each of the descriptors for modeling the activity. The modeling will be effectively carried out using softwares: Regress-1 (36), martha (39), origin (40) and NCSS. Finally, the proposed QSAR models will be cross validated by leave-on-out procedure.

RESULTS AND DISCUSSION

The results obtained in the present study for modeling antimalarial compounds on the basis of topological indices J, R, F and G. The value of J indices was calculated using DRAGON software and the value of R, F, and G has calculated by Balban indices J. The values of J, R, F and G have been given in Table 2.

Application of rule of thumb for the set of 20 peroxy cetals used in the present investigation has indicated that we can use at the most four parameters (topological indices) for modeling the antimalarial activity. By using leave out method, the data presented in Table 2 can be divided into two different categories. First category contains 20 compounds and the other contains 19 compounds. The application of stepwise regression indicated that category 1 contain 20 compounds. Following model is the most appropriate model for modeling of anti malarial activity of compounds.

$$\text{Log } (IC_{50}) = -5.2304 + 7.5122\ (\pm\ 4.0192)\ J - 1.4915\ (\pm\ 1.1146)\ F - 3.0376\ (\pm\ 2.0831)\ NSK + 2.943\ (\pm\ 2.0820)\ NBO \quad \ldots(7)$$

Where N = 20; CV = 0.0902; $R^2 = 0.7092$; $R^2A = 0.6317$ and F = 11.051

In the above model, F is the correlating parameter. Its negative coefficient indicates that decrease in shape is favourable for the exhibition of antimalarial activity. Also that the model explains 70% variance in the anti malarial activity.

The category 2 is also having same parameters of category 1, which are J, F, NSK and NBO, which are given below:

$$\text{Log } (IC_{50}) = -5.8754 + 7.8906\ (\pm\ 3.5203)\ J - 1.5391\ (\pm\ 0.95752)\ F - 3.2467\ (\pm\ 1.8261)\ NSK + 3.194\ (\pm\ 1.8255)\ NBO \quad \ldots(8)$$

Where N = 19; CV = 0.0782; $R^2 = 0.7754$; R^2 A = 0.7112 and F = 9.416.

This model contains F parameter with negative coefficient indicating that antimalarial activity of compounds belonging to this category increase with decrease in the shape of the molecule and accounts for 78% of variance of data. After the Ridge analysis, the parameters indicates that the model is free from defect due to colinearity.

It is normally recommended that for obtaining appropriate model, N should be as large as possible. The coefficient of variance, CV should be as small as possible. R^2 is actually square of correlation coefficient and in obtaining the best model, R^2 should be as near to 1 as possible.

In order to confirm the results obtained through model discussed above, we have estimated antimalarial activity and correlated with the observed i.e. experimental activity. Such a correlation is shown in following category Figs. 1 and 2 indicate that both observed and estimated activity are close to each other.

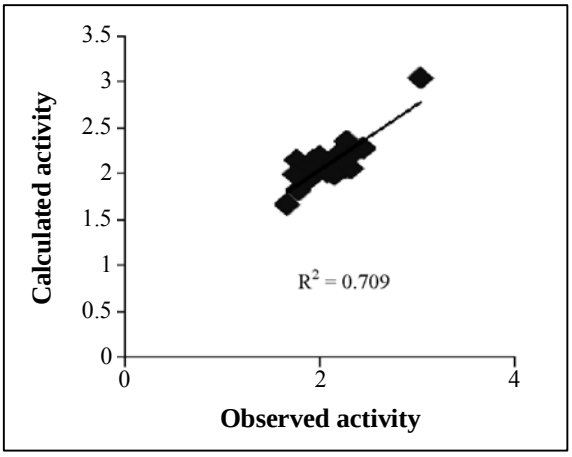

Fig. 1:

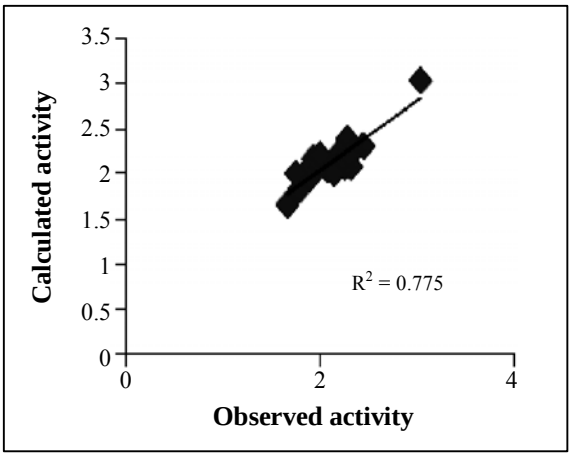

Fig. 2:

CONCLUSION

The results obtained here indicate that the newly introduced F index in combination with J index can be successfully used for modeling antimalarial activity of peroxy cetals used.

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