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TOPOLOGICAL MODELING OF ANTICANCER ACTIVITY OF AZA-18-CROWN-6 ETHERS AND ITS DERIVATIVES

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ABSTRACT

The paper describes QSAR studies on anticancer activity using Topological descriptors and constitutional descriptors. A series of 16 known mono aza and di aza-18-crown-6 ethers derivatives were used as anticancer or various human cancer cell lines inhibitors. Topological parameters such as Molecular weight (MW), Sum of Sanderson electro negativities (Se), Polarity number (Pol), Mean square distance (Balaban Index) MSD, Schultz molecular topological index (SMTI), Schultz molecular topological index Valence vertex degree (SMTIV) are used. Biological activity of these compounds varies depending on the molecular structure. These crown ethers were screened for their potential antiproliferative effect on cancer cell. The regression analysis data has shown that 'MW' plays a dominating role in modeling of logP of present set of compounds. SMTIV also play a dominant role in proposed four parametric model gives excellent Result. The Anticancer activity is expressed as (logP).

Keywords- *Anticancer activity (logP), MW, Topological modeling, QSAR.*

I. INTRODUCTION

Crown ethers exhibit ionophoric properties in membranes due to its characteristics structures, which makes crown ethers particularly interesting and useful in chemical and biological research and their pharmaceutical potential remain large naturally occurring Ionophores [1, 2]. 18-crown-6 ethers are known to exert their biological activity by transporting K^+ ions across cell membranes. Using non-linear Support Vector Machines regression, Fran Supek and coworkers [3] searched for structural features that influence antiproliferative activity in a diverse set of known oxa-, mono aza- and diaza-18-crown-6 ethers.

They showed that the log P which is also an important lipophilicity parameter used to understand the activity of any drug molecule is the most important molecular descriptor, among ~1300 tested descriptors, in determining biological potency.

They also proposed a QSAR model and synthesized six novels, highly lipophilic diaza-18-crown-6 derivatives with adamantane moieties attached to the side arms for the validation of the proposed model. These compounds have near-optimal log P values and consequently exhibit strong growth inhibition in various human cancer cell lines and a bacterial system.

In the present paper modeling of some aza-18-crown-6 ethers derivatives with Anti cancer activity (logP) of a diverse set of 16 known oxa-mono aza and di aza-18-crown-6 ethers. Using Topological parameters.

II. MATERIALS AND METHOD

In Quantitative structure activity relationship (QSAR) studies the lipophilicity /Anti cancer activity expressed as logP. We have developed a mathematical model using multiple regression analysis [4].

$Y = m x + c$ …….. (1)

Y= biological activity, x = independent parameters and c = intercept.

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Topological indices used in present study

1. Molecular Weight (MW)
2. Sum of Sanderson electro negativities (Se)
3. Polarity number (Pol)
4. Mean square distance (Balaban Index) MSD
5. Schultz molecular topological index (SMTI)
6. Schultz molecular topological index Valence vertex degree (SMTIV)

We have calculated topological parameters by using Dragon software [5]. The calculated parameters are reported in Table 1.

III. RESULT AND DISCUSSION

In our present work the QSAR studies or Topological modeling of a divers set of di aza 18-crown-6 ethers with corresponding adamantane derivatives by using an approach on the literature procedure [6]' Biological activity of these compounds varies depending on the molecular structure, these crown ethers were screened for their potential anti proliferative effect on a panel of seven human cell lines, which were derived from different cancer types which expressed in GI_{50}, but for best modeling anti proliferative logP is calculated by Ghose-crippen method [7] which is based on non linear regression model . Adamantane crown ethers (1to16) would strongly inhibit the growth of cultured cancer cell. This is shown in Table 1.compound no, 1 showed very modest anticancer activity, due to presence of long alkyl side-chain attached to benzene ring. While Unsubstituted mono and di aza 18-C-6 (Comp. no. 3, 9) did not show anti cancer activity. On other hand substituted aza-18-C-6 (adamantane molecules) shows higher activity. No 1:1 correlation has been found in the activity and structure of the compounds. The structures of molecules were drawn from Chem. Sketch ACD/Labs software (11.01) version [8].

Table 1: Value of Lipophilicity (logP) and calculated Value of descriptors used

No.	LOGP	MW	Se	Pol	MSD	SMTI	SMTIV
1	17.6	781.198	84.802	48	8.708	17428	24726
2	1.06	353.51	55.992	29	6.565	7282	11363
3	-1.05	263.38	43.342	18	5.363	2988	4858
4	0.49	384.57	62.869	42	6.125	8474	11974
5	2.28	425.68	72.294	41	7.338	12332	16624
6	2.74	439.628	74.928	42	7.748	13223	17524
7	1.33	439.66	71.738	44	7.267	13006	18459
8	1.79	453.69	74.621	45	7.722	14654	20578
9	-1.32	262.4	44.116	18	5.363	2988	4688
10	5.35	587	102.021	64	10.065	34168	40076
11	6.25	615.06	107.788	66	10.952	40448	47056
12	3.45	614.96	100.908	70	10.037	37180	47692
13	4.36	643.02	106.675	72	10.893	43772	55424
14	3.384	586.9	95.141	72	9.187	31260	40700
15	4.703	558.94	96.254	62	9.18	28540	33788
16	1.77	504.78	83.17	66	7.633	19672	24632

We have tried variable selection method by NCSS Software [9] to get multi-parametric correlations and the results are reported in Table-2. Mw is highly correlated to Pol, SMTI and SMTIV. Also plays a dominating role in four parametric models using maximum R^2method.

Table 2: Variable selection Report

Model Size	R-Squared	R-Squared Change	Variable Names
1	0.714430	0.714430	MW
2	0.969212	0.254782	MW, Pol
3	0.981823	0.012612	MW, Pol, SMTIV
4	0.995239	0.013415	MW, Pol, SMTI, SMTIV
5	0.995640	0.000401	MW, Se, Pol, SMTI, SMTIV
6	0.996430	0.000790	MW, Se, Pol, MSD, SMTI, SMTIV

We have also obtained a correlation matrix which shows that how the parameters are correlated which is reported in Table 3.

Table 3: Correlation Matrix

	MW	Pol.	SMTI	SMTIV	LOGP
MW	1				
Pol.	0.807615	1			
SMTI	0.782707	0.915832	1		
SMTIV	0.804064	0.920978	0.995421	1	
LOGP	0.84524	0.384967	0.386074	0.404927	1

This analysis also tells us whether some of the parameters are highly correlated and they may give some models which may suffer from the defect of collinearity.

For a set of 16 compounds one can use only three parameters for modeling the log P. Systematic modeling gave many statistically significant correlations. The quality of such correlations is reported in Table 4. As discussed above, The 'MW' plays a dominating role in modeling of log P of present set of compounds. Similarly 'SMTIV' Also plays a dominant role in four-parametric model using maximum R^2 method.

Estimated model:

log P = 0.0504(±0.0012)MW - 0.1538(±0.0133) Pol.+ 0.0004(±0.0001) SMTI - 0.0004(±0.0001) SMTIV - 10.7811 …… (4)

N=16 Se=0.4194 R^2=0.9952 R^2_A=0.9935 F=574.853 Q=2.3786

The four-parametric model is found to be best among all the models discussed above.

Table 4: Regression Parameters and quality of correlations of obtained Models.

Model No.	Para-Meters Used	Ai=(1-----3)	B	Se	R^2	R^2 Adj.	F	Q=R/Se
10	MW Pol. SMTI SMTIV	0.0504(±0.0012) -0.1538(±0.0133) 0.0004(±0.0001) -0.0004(±0.0001)	-10.7811	0.4194	0.9952	0.9935	574.853	2.3786

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To confirm this finding we have calculated log P values of the present set of the compounds using the best four-parametric model. A good agreement in estimated Alog P with actual values confirmed the finding. Such values are reported in Table 4.2.6

A graph has been plotted using observed logP and estimated log P. Such comparison is demonstrated in Fig-1. The predictive power of the model comes out to be 0.995, which shows that this model explains 99% of Variance of the data used in the present study.

Table 5: Observed and estimated logP values using model 10.

Compd. No.	Observed AlogP	Estimated AlogP	Residual
1	17.600	17.546	0.054
2	1.060	0.593	0.467
3	-1.050	-1.176	0.126
4	0.490	0.381	0.109
5	2.280	2.158	0.122
6	2.740	2.680	0.060
7	1.330	1.876	-0.546
8	1.790	2.179	-0.389
9	-1.320	-1.151	-0.169
10	5.350	5.468	-0.118
11	6.250	6.103	0.147
12	3.450	3.860	-0.410
13	4.360	4.294	0.066
14	3.384	2.763	0.621
15	4.703	4.798	-0.095
16	1.770	1.813	-0.043

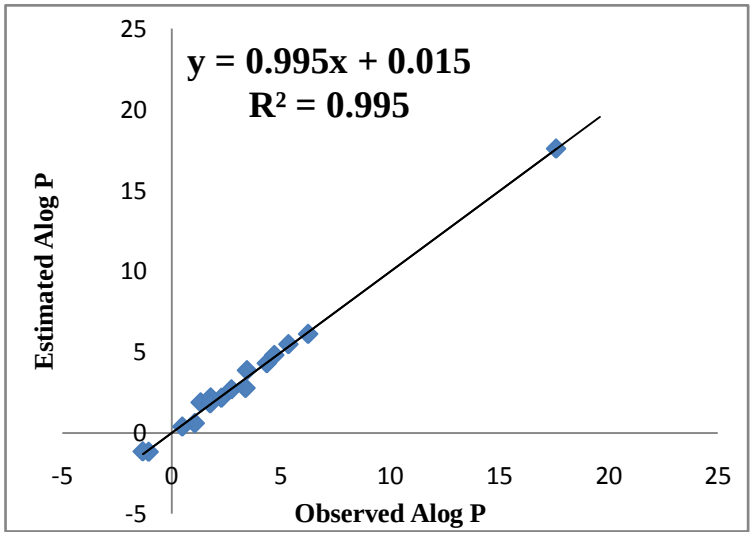

Fig-1:Correlation between Observed and Estimated LOGP values Using four parametric model.

The model has also been tested by obtaining Cross Validated parameters. It is argued that PRESS is a good estimate of the real prediction error of the model and if it is smaller than SSY the model predicts better than chance and can be considered "statistically" significant. All cross-validated parameters given in Table 6.

Table 6: Cross Validated parameters for the obtained models

S. No.	Parameters Used	PRESS/SSY	R^2_{cv}	S_{PRESS}	PSE
1	MW	149.0992/30.636	0.4740	3.22634	3.05265
2	MW, Pol.	30.2949/15.044	0.8931	1.5265	1.3760
3	MW Pol. SMTIV	9.0841/9.406	0.9679	0.8700	0.7534
4	MW Pol. SMTIV SMTI	0.76624	0.9832	0.6586	0.5461

R> 6PE, then the correlation is definitely good.

The data presented in Table 6. indicates that in all the cases R is much larger than 6 PE indicating that all the proposed models have very good correlations. To test whether the four parametric model is free from any kind of defect Ridge analysis has been carried out. The ridge trace is shown in Fig 4.2.3. All the parameters are with the permissible limits.

Table 7: Ridge regression parameters for the best models

S. No.	Parameters Used	VIF	T	λi	K
4	MW Pol. SMTIV SMTI	2.9817 6.5794 27.3215 25.0707	0.2912 0.1384 0.0074 0.0082	3.6183 0.2750 0.1026 0.0039	1.00 13.15 35.25 915.83

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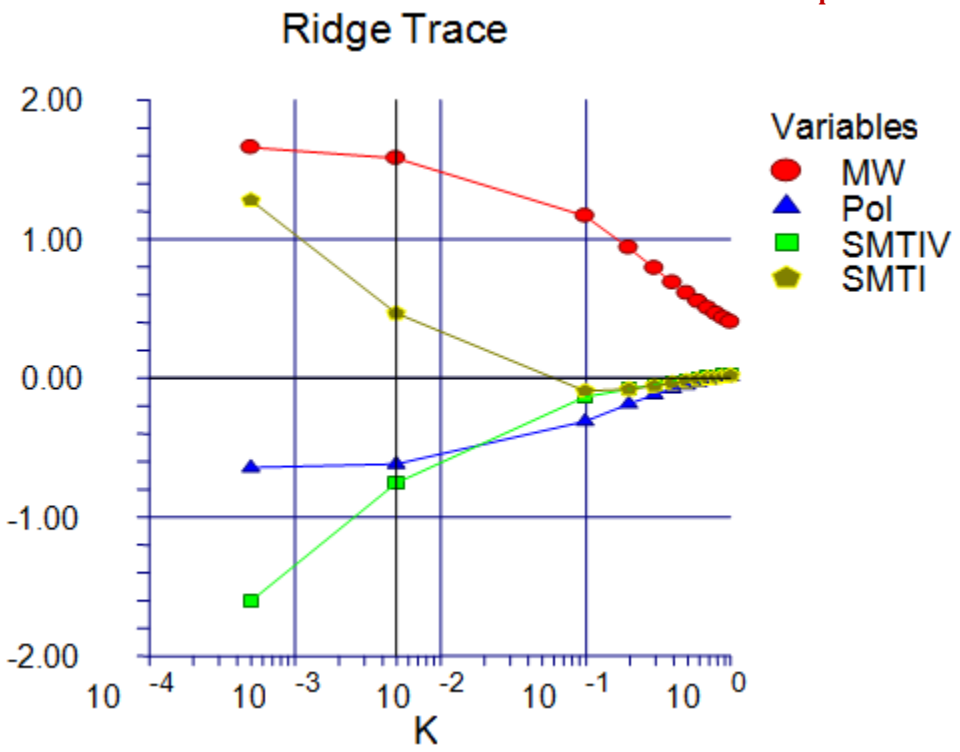

Fig-2. Ridge Trace for four parametric model no.10

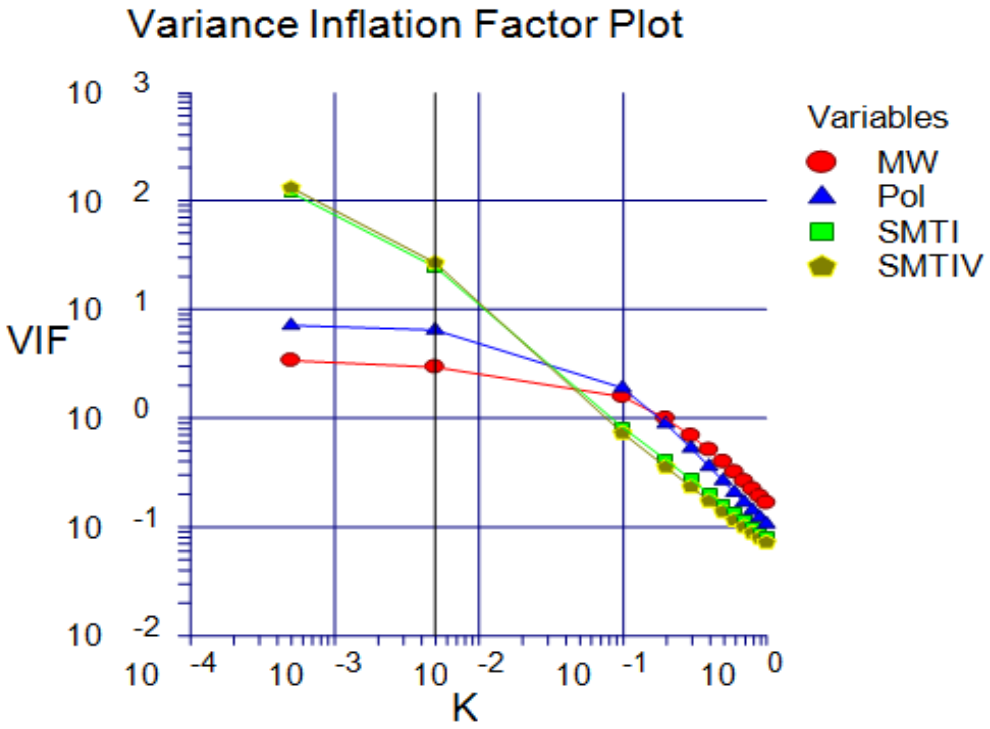

Fig-3. VIF plot for the obtained four parametric model.

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IV. CONCLUSIONS

On the basis of obtained result following conclusions may be drawn:

1. No mono-parametric model is able to predict the log P value of present set of Compounds.
2. The parameter MW has a positive coefficient in the four-parametric model suggesting that molecular weight will favor the exhibition of log P.
3. The parameter SMTIV also plays a dominating role and has a positive coefficient suggesting that it has a favorable role towards activity.
4. Therefore in obtaining a better active molecule the structure with higher value of MW and SMTIV will be preferred.

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