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Modeling of sulfonamide using NMR chemical shift by QSDAR Method

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Abstract- The paper describes the estimation of chemical shifts in NMR using Balaban and Balaban type indices. Further attempt is made of using NMR chemical shift along with the above indices for modeling carbonic anhydrase inhibition. The statistically significant models are governed by a variety of statistical parameter.

Key Words : QSAR Method, Carbonic Anhydrase Inhibition activity. Topological Indices, NMR Chemical Shift

Introduction

Carbonic acid anhydrase are zinc containing enzymes present in green plants and animals. They are responsible for interconversion of carbonic acid and carbon dioxide to bicarbonates and H_3O^+. Carbonic anhydrase II (CA II) catalyses the reversible hydration of carbon dioxide through a two step zinc hydroxide mechanism 1,2

$Zn - OH^- + CO_2 + H_2O \leftrightarrow Zn - H_2O + HCO_3^-$

$Zn - tho \leftrightarrow Zn - OH^- + H^+$

They play an important role in several physico pathological processes that include the blood transport of CO_2, the formation of HCl in the stomach, and elevated pressure of the aqueous humor in eyes (Glaucoma)[1-3]. In early 1940 attempt were made towards the synthesis and subsequent screening of sulfonamides possessing carbonic anhydrase inhibitory characteristics. When the enzyme is inhibited,the generation of carbonic acid (H_2CO_3) that usually dissociate into HCO_3^- and H_3O^+ is also inhibited. This results in the excretion of large quantity of urine and hence diuresis.[4]. Therefore, sulfonamides that inhibit carbonic anhydrase enzyme possess many applications as diuretic, antiglucoma, antiepileptic and antithyroid drugs. Supuran and coworkers[5] have synthesized a series of water soluble sulfonamides having picolinoyl moieties. These derivatives were found to be inhibitors of three carbonic anhydrase (CA) isozymes, CA I, II (Cytosolic forms) and IV (membrane bound form) and were found to be very strong intraocular pressure (IOP) lowering agents for glaucomatous albine rabbits. Sapuran and his team also prepared dorzolamide derivative to which the picolinoyl moiety was attached. This new compound was found to be more water soluble than dorzolamide, behaves as a strong CA II inhibitor and acts similarly to the parent derivative in lowering IOP in experimental animals. Thus, it seems that the tail (in this case picolinoyl moiety) conferring water solubility in more important to topical activity as antiglaucoma drug than the heterocyclic/aromatic ring to which the sulfamido moiety is grafted.

Topological indices and NMR chemical shift information of compounds can be combined to form models of biological activity. Quantitative spectroscopic data_activity_relationship (QSDARs) models are based on determining a relationship between the NMR spectra of a set of molecules and their biological activities. A novel use of chemical shift of the $-SO_2NH_2$ protons as a molecular descriptor was described by Khadikar and coworkers for modeling the carbonic anhydrase inhibition constant of benzene sulfonamides[6-8]. The same author has shown the use of ^{13}C NMR chemical shift for modeling lipophilicity (log P) of alcohols[9]

Prompted by the above work we have undertaken the present study in that we have modeled carbonic anhydrase inhibition activity $\log K_i$ using NMR chemical shift of some benzene sulfonamides containing picolinoyl moieties. The objective of the present study is two fold, that is, to investigate modeling of carbonic anhydrase inhibition activity by using NMR chemical shift(δ) of $-SO_2NH_2$ proton together with a variety of graph theoretical indices in different combinations and to model chemical shift (δ) by using Balaban and Balaban type indices.

Material and Methods

The series of 21 sulfonamides used by us are shown in Table 1. The log K_i and NMR chemical shift values of these compounds are taken from literature[6]. In table 2 the values of their carbonic anhydrase inhibition,

NMR chemical shift is reported. The various graph theoretical descriptors used by us are as follows:

Balaban and Balaban type Indices : J, $J_{net2,}$ J_{netm}, J_{nete}, J_{netv}, J_{netp}

The Balaban and Balaban type indices of these compounds are given in Table 3. All these descriptors are calculated using DRAGON software. The structure optimization was done using ACD labs software.

In QSAR analysis they normally stand for certain structural features not covered under the molecular descriptors used. Free Wilson analysis may be interpretated as a regression analysis approach using parameters [14,15,17].The multiple regression analysis was done by Data Analysis. For getting good multiparametric model we have carried out successive regression analysis and adopted the method of maximum R^2 [18,19]. The maximum R^2 method tries to switch an included variable with an excluded variable which provides the largest increase in R^2. This process continues until no included variable can be switched that would increase R^2. The resulting model is said to be the best model for that level of explanatory variables.

Results and Discussions

As mentioned above the objective of the present study is to model logk; by using NMR chemical shift (δ) and graph theoretical descriptors as well as to model NMR chemical shift by using Balaban and Balaban type indices.

Modeling Chemical Shift (δ) using Balaban and Balaban Type indices

Balaban Index (J) is highly discriminating index and it can be weighted easily yielding different types of Balaban indices. We have used J_{hetz} (Balaban type index from z weighted distance matrix), J_{hetm} (Balaban type index from mass weighted distance matrix), J_{hetv} (Balaban type index from Van der Waal's weighted distance matrix), J_{hete} (Balaban type index from electro negativity weighted distance matrix) and $J_{het\ p}$ (Balaban type index from polarisability weighted distance matrix). Khadikar et al. [20-22] have used this index successfully in developing some QSPR/QSAR models. Furthermore the same author, in collaboration with Balaban recently have undertaken a project for investigating the role of Balaban and Balaban type indices in developing QSPR/QSAR/QSTR models [23-25]. The use of Balaban index in QSAR studies remained ineffective up to 2001 due to unavailability of appropriate software for calculating this index. In 2001 Lukovits provided his LUKO-1 software for calculation of Balaban index. The calculations of Balaban type indices were made easy by the advent of DRAGON software.

A regression analysis using Balaban and Balaban type indices is done to model (δ) models showing good statistics were selected by NCSS software[26]. Table 5 shows that the quality of the models goes on increasing with addition of indices. Third model is not statistically significant as some of the coefficients are less then the respective standard deviations. The hexaparametric model is found to be the most suitable model among all the six models.

$\delta = 9.2592\ (\pm\ 1.0537) + 283.6294\ (\pm 189.6604)\ J_{het\ z} - 6.5704\ (\pm\ 3.0186\ )\ J + 20.7873\ (\pm 10.1862\ )\ J_{het\ p} - 20.7354\ (\pm\ 12.1207)\ J_{hetv} + 8.4237\ (\pm\ 3.8158)\ J_{hete} - 286.921\ (\pm 189.6146\ )\ J_{hetm}$

n=21, R=0.7405, Se = - 4378, F = 2.8331 Q=1.6914

The relationship of number of parameters Vs R^2 and R^2A is shown in fig.1.

Modeling log Ki using Balaban and Balaban type indices:

The regression parameters and quality of correlations is shown in Table 4. The penta- and hexa-parametric models were found to be statistically insignificant Tetraparametric model is better then other models.

$\log K_i = - 4.3477\ (\pm\ 1.7856) + 13.4524\ (\pm\ 3.1306) J + 475.2729\ (\pm\ 303.2544)\ J_{hetz} - 480.1132\ (\pm\ 303.3338)\ J_{hetm} - 2.3101\ (\pm 1.8384)\ J_{het\ v}$

n=21 R= 0.7977 Se = 0.7461 F=7.0015 Q= 1.0692

Predictive Powers of the proposed models:

We now discuss the predictive powers of each of the best models. Model no.1 models NMR chemical shift δ where as model no.2 model CA inhibition activity log ki. The best way to investigate the predictive powers of the models is to calculate poglian's quality factor Q . It if defined as the ratio of the correlation coefficient R to the standard error of estimation.

$$Q = \frac{R}{Se}$$

Higher the value of Q, better will be the predictive power of the model.the perusal of table 5 shows model no.2 have excellent predictive powers. The predictive property of all these models can also be judged by estimating residue i.e. the difference between the observed and calculated activity (Table 6) .

Model Validation

Cross Validation is a practical and reliable method for testing the significance of a model. The cross validation parameters often used being PRESS (Predicted residual

sum of squares), SSY (sum of the squares of the response value), R^2_{cv} (Cross validated R^2 or overall predictive ability), PSE (predictive square error) and PE (Probable error of the coefficient of correlation.

It is argued that PRESS is a good estimate of the real predictive error of the model. It is given by the formula

$$PRESS = \Sigma(Y_{est\_} Y_{obs})^2$$
$$SSY = \Sigma (Y_{obs} - Y_{mean})^2$$

If PRESS is smaller than SSY, the model predicts better than chance and can be considered statistically significant. The ratio PRESS/SSY can be used to calculate approximate confidence intervals of prediction of new observations (compounds). For a good model the ratio PRESS/SSY should be smaller than 0.4. If this ratio is smaller than 0.1, the model is considered to be excellent. A perusal of the table 12 shows model no.2 and 6 have values 0.0970 and 0.1160 respectively indicating them to be far better than other models.

Probable error of correlation coefficient denoted by PE is an old measure of testing the reliability of an observed value of correlation coefficient in so far as it depends upon the conditions of random sampling. PE is given as

$$PE = 0.6745 \times \frac{1 - R^2}{\sqrt{n}}$$

Where R is correlation coefficient, n is number of compounds used. The reason for taking 0.6745 is that in a normal distribution 50% of the observations lie in the range $\mu \pm 0.6745\ \sigma$, where μ is the mean and σ is the standard deviation.

PE may be used to test if an observed value of sample correlation coefficient is significant of any correlation in the population

1) R < PE, then the correlation is not at all significant.
2) R>6PE, then R is definitely significant
3) In other situations nothing can be concluded with certainty.

A perusal of the table 6 shows R is greater than 6PE in all the cases indicating all correlation attempts are definitely good. It is worth mentioning that the values of PE for model no.2 are excellent compare to other models.

Another cross validated parameter of interest is the predictive correlation which is generally named as cross validated R^2 or R^2_{cv}. The highest values of R^2_{cv} indicates the best predictive power. Once again R^2_{cv} is in favour of model no.2 .

Conclusion

From the aforementioned results and discussion we conclude the following:

1) log ki can be excellently modeled by models 2.
2) Model 6 has correlating parameters , $J_{hetm,}$ J and J_{hetp}. This shows NMR chemical shift together with Balaban can very well model log ki.

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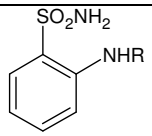
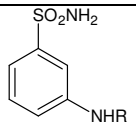
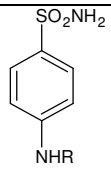
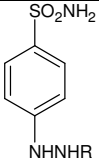
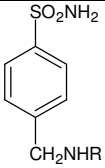
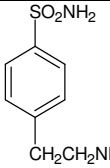
Table 1 . Structural details of carbonic anhydrase inhibitor used in present investgation

 1. R= Picolinoyl	 2. R= Picolinoyl	 3. R= Picolinoyl
		

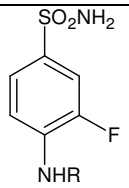
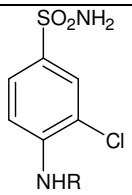
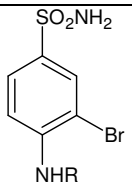
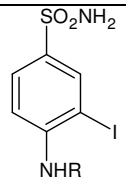
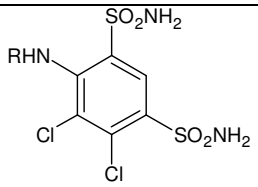
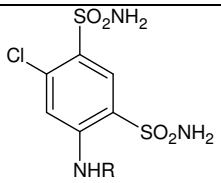
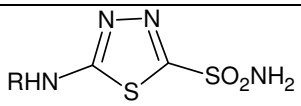
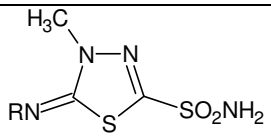
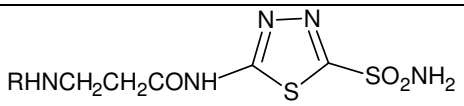
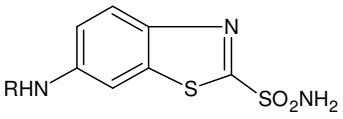
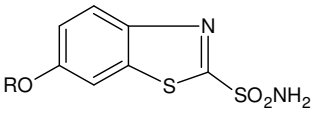
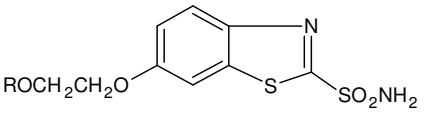
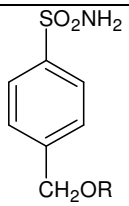
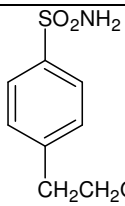
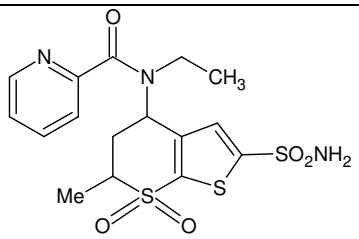
4. R= Picolinoyl	5. R= Picolinoyl	6. R= Picolinoyl
 7. R= Picolinoyl	 8. R= Picolinoyl	 9. R= Picolinoyl
 10. R= Picolinoyl	 11. R= Picolinoyl	 12. R= Picolinoyl
 13. R= Picolinoyl	 14. R= Picolinoyl	 15. R= Picolinoyl
 16. R= Picolinoyl	 17. R= Picolinoyl	 18. R= Picolinoyl
 19. R= Picolinoyl	 20. R= Picolinoyl	 21. R= Picolinoyl

Table 2 . log Ki, and chemical shift used in the present study.

Compoud No.	LogKi	$\Delta(SO_2NH_2$
1	4.33	7.50
2	4.29	7.60
3	4.17	7.56
4	4.35	7.59
5	3.04	7.67
6	3.04	7.67
7	2.72	6.60
8	2.78	6.70
9	2.79	6.65
10	2.78	6.60
11	2.71	7.68
12	2.78	7.75
13	1.60	6.94
14	1.49	6.96
15	1.30	6.88
16	1.00	8.10
17	1.04	8.10
18	1.00	8.15
19	3.32	7.49
20	3.31	6.95
21	3.20	8.25

Table 3 .The values of Balaban and Balaban type indices of the Carbonic anhydrase inhibitor used in the present study

Comp. No.	J	Jhetv	Jhetm	Jhete	Jhetz	Jhetp
1	1.811	1.426	2.697	2.461	2.697	1.316
2	1.725	1.391	2.564	2.374	2.564	1.285
3	1.652	1.369	2.453	2.283	2.453	1.257
4	1.591	1.215	2.335	2.19	2.336	1.098
5	1.591	1.329	2.243	2.111	2.243	1.237
6	1.539	1.304	2.082	1.976	2.082	1.220
7	1.736	1.407	2.576	2.400	2.575	1.294
8	1.736	1.432	2.594	2.395	2.594	1.329
9	1.736	1.438	2.607	2.392	2.606	1.333
10	1.736	1.440	2.611	2.385	2.61	1.338
11	2.083	1.784	3.296	2.866	3.296	1.711
12	1.994	1.697	3.141	2.744	3.14	1.623
13	1.682	1.311	2.841	2.361	2.842	1.234
14	1.758	1.365	3.019	2.429	3.019	1.297
15	1.539	1.210	2.163	1.954	2.163	1.134

16	1.426	1.245	2.293	2.017	2.293	1.177
17	1.426	1.100	2.365	2.074	2.365	1.018
18	1.277	0.924	1.932	1.762	1.932	0.851
19	1.591	1.176	2.306	2.169	2.307	1.074
20	1.539	1.164	2.133	2.023	2.133	1.070
21	1.840	1.875	2.660	2.295	2.660	1.906

Table 4 . Modeling of chemical shift using Balaban and Balaban type indices

Parameters used	Se	R^2	R^2_A	F
J_{hetv}	0.5592	0.0500	0.0526	0.0001
J, J_{hetp}	0.4844	0.3685	0.2099	3.6577
J, J_{hetv}, J_{hetp}	0.4902	0.3123	0.1910	2.5741
J, J_{hetze}, J_{hetp}, J_{hetv}	0.4842	0.3685	0.2107	2.3348
J, J_{hete}, J_{hetm}, J_{hetv}, J_{hetp}	0.4555	0.4762	0.3016	2.7276
J, J_{hetz}, J_{hetm}, J_{hetv}, J_{hetp}, J_{hete}	0.4682	0.4102	0.3310	2.5767

Table 5. Modeling logKi using Balaban and Balaban type indices

Parameters used	Se	R^2	R^2_A	F
J	1.0415	0.1587	0.1144	3.5846
J_{hetm}, J_{hetv}	1.0628	0.1699	0.0776	1.8424
J_{hetz}, J_{hetm}, J_{hetv}	1.0623	0.2168	0.0786	1.5688
J, J_{hetz}, J_{hetm}, J_{hetv}	0.7461	0.6364	0.5455	7.0015
J, J_{hetz}, J_{hetm}, J_{hetv}, J_{hetp}	0.6380	07507	0.6676	9.6365
J, J_{hetz}, J_{hetm}, J_{hetv}, J_{hetp}, J_{hete}	0.6441	0.7629	0.6612	7.5080

Table 6 . Observed and Calculated values of logKi from Eqn. No. 2

Comp. No.	logKi	Calcu. logKi	Residual
1	4.33	4.039502	0.290498
2	4.29	3.711672	0.578328
3	4.17	3.813534	0.356466
4	4.35	3.732119	0.617881
5	3.04	3.686516	-0.64652
6	3.04	3.574363	-0.53436
7	2.72	2.941606	-0.22161
8	2.78	2.825624	-0.04562
9	2.79	2.69642	0.09358
10	2.78	2.60658	0.17342
11	2.71	3.029903	-0.3199
12	2.78	2.498686	0.281314
13	1.6	1.533235	0.066765
14	1.49	1.775165	-0.28516

15	1.3	1.081759	0.218241
16	1	1.197605	-0.1976
17	1.04	1.206739	-0.16674
18	1	0.741608	0.258392
19	3.32	3.658439	-0.33844
20	3.31	3.595466	-0.28547
21	3.2	3.094142	0.105858

Fig. : Modeling logKi using Balaban and Balaban type indices

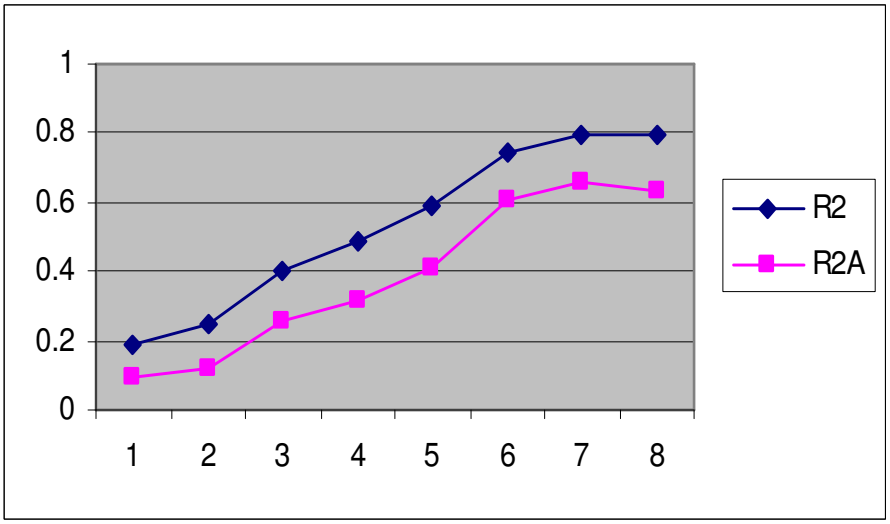


Fig. : Modeling Chemical Shift (δ) using Balaban and Balaban Type indices