Abstract:-

The rate of glycine conjugation (M,n mol/mg protein) of series of benzoic acid derivatives in rat liver (log Mliv) and kidney (log Mkid) was modeled using a set of molecular descriptors including distance-based topological indices. Simple as well as multiple regression were performed to generate the equations (models) that relates the structural features (molecular descriptors/ topological indices) to biological activities: log Mliv and log Mkid. The regression analysis indicated that the best model for prediction of the rate of glycine conjugation is obtained in multipara metric regression, which included the indicator parameters. The result are critically discussed using cross-validated parame ters.

Keywords:

Glycine, Conjugation, log Mliv, log Mkid, and topological atc.

ON THE RATE OF GLYCINE CONJUGATION OF SOME BENZOIC ACID DERIVATIVES : A TOPOLOGICAL APPROACH

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INTRODUCTION

The amino acid glycine is utilized is mammalian systems to conjugate carboxylic acid particularly aromatic acids. Glycine conjugation is common to most mammals. The quantity Glycine conjugation formed from xenobiotics is quite small because of limited availability of glycine in the body and substrate is activated with ATP and Coenzyme-A to from an acyl Coenzyme-A complex.

The later intermediate in turm acylates glycine under the influence of specific glycine N-acyl trasfarase enzymes. The activation and acylation steps take place in the mitochondria of liver kidney cells. Amino acid conjugation being polar and water soluble, is mainly excreted renally and sometime in the bile. Aromatic acid are the major subtrates undergoing glycine conjugation. The conversion of benzoic acid to its glycine conjugate, hippuric acid is a well known metabolic acid reaction of hydrolysis of many drugs are also susceptible to glycine conjugation. It is worthy to mention that metabolism plays a central role in the elimination and other foreign compound from the body.

At this stage it is Important to mention that conjugation with glycine proceed through ATP dependent of coupling of carboxylic acid with coenzyme (Co-A). Therefore, chemicals that from Co-A esters many interfere with glycine conjugation, the conjugation of aromatic carboxylic acid, such benzoic acid and its nuclear substituted derivatives, which are the best candidates to be investigated for the purpose glycine conjugation.

Quantitative Structure Activity Relationship (QSAR) studies are now a day applied in drug designing[1-10]. The primary aim of such a study is the optimization between physiological and structure of a series of organic compounds acting as drugs. This is more conveniently performed by variation in the substitution pattern. According to Hansch methodology hydrophpbic, and steric parameters of the substituents are the main parameters used in QSAR studies6. Consequently, Hansch methodology does not give 1:1 correlation between structure and activity. The use of topological method proved to be more promising as it used topological indices, which are considered as numerical representation molecular structure. Thus, topological drug designing provides 1:1 correlation between structure and activity[7-9]. Our earlier studies have shown that distance based topological indices are better for this purpose. In addition, we have observed that some combination of topological indices with other molecular descriptors can also be used successfully in QSAR studies[10-11].

In view of above we have undertaken present study in that relationship between the chemical structure and glycine conjugation of benzoic acid derivatives (Table 1) in the rate liver (log Mliv) and kidney (log Mkid) mitochondria have been investigated. Here, M_{liv} and M_{kid} represents the of glycine conjugation in liver and kidney respectively. These quantities are adopted from literature[12] and the result as discussed below show that both log M_{liv} and log M_{kid} be modeled exceliently in multi-parametric regression analysis[13-15] using topological indices in combination with some indicator parameters.

EXPERIMENTAL :-

Activity data : Both log M_{liv} and log M_{kid} data have taken from the literature.

Topological Indices : All the topological indices were calculated from the hydrogen suppressed graphs in that all the carbon-hydroge as well as hetro atom-hydrogen bonds were deleted from the molecular structurte. The calculations of these indices are well documented in the literature and thus they are not mentioned here. The details of calculations of Wiener index (W), First-order connectivity index (^1X), Balaban index (J), Szeged indexes (Sz), log (RB) and W* are given references.

RESULT AND DISCUSTION :-

The structural details of benzoic acid derivatives with adopted values of log Mliv and log Mkid and assumed indicator parameters are given in Table 1. The indicator parameters Ip_1, Ip_2 and Ip_3 accounts for the substitution at 3-position, 4-position and di-substitution respectively. The indicator parameters assume only two values i.e. 1 (one) when the structural features are present in the molecule and 0 (zero) when these are absent. On the basis of log Mliv and log Mkid values the following sequence of rate of glycine conjugation of benzoic acid derivatives have been used.

Table -1
compouds use in present study with their log Mkid and log Mliv values and indicator values.

S.No.	Compouds	log Mkid	log Mliv	Ip_1	Ip_2	Ip_3
1	Benzoic acid	1.44	1.28	0	0	0
2	4-Cl Benzoic acid	1.57	1.59	0	1	0
3	4-CN Benzoic acid	1.27	0.62	0	1	0
4	4-NO_2 Benzoic acid	1.02	0.79	0	1	0
5	4-NH_2 Benzoic acid	0.79	0.59	0	1	0
6	4-NH_2COCH3 Benzoic acid	-0.64	-0.08	0	1	0
7	4-$N(CH_3)_2$ Benzoic acid	0.08	0.17	0	1	0
8	4-CH_3 Benzoic acid	1.49	1.56	0	1	0
9	4-CH_3O Benzoic acid	1.00	1.09	0	1	0
10	4-OCH_2CH_3Benzoic acid	.089	0.92	0	1	0
11	3-Cl Benzoic acid	1.79	1.57	1	0	0
12	3-CN Benzoic acid	0.95	0.69	1	0	0
13	3-NO_2 Benzoic acid	1.23	0.73	1	0	0
14	3-NH_2 Benzoic acid	1.45	0.76	1	0	0
15	3-NHCOCH3 Benzoic acid	-0.10	-0.29	1	1	0
16	3-$N(CH3)_2$Benzoic acid	0.45	0.20	1	0	0
17	3-CH_3 Benzoic acid	1.83	1.71	1	0	0
18	3-OCH_3 Benzoic acid	1.35	1.34	1	0	1
19	3$OCH_2CH_2CH_2CH_3$4NH2 Benzoic acid	-0.2O	0.23	1	0	1
20	3-OH,4-OCH_3Benzoic acid	0.79	0.46	0	0	1
21	3-OH, 4- NO_2Benzoic acid	0.61	0.81	0	0	1
22	3-NO_2,4-Cl Benzoic acid	0.06	-0.16	1	0	1

TABLE -2
Values of topological indices calculated for the compounds used.

Compounds	W	^1X	J	Sz	log(RB)	w*
1	88	4.3045	2.2283	142	27.6625	176
2	120	4.6983	2.2599	192	37.8252	262
3	162	5.2363	2.2427	252	50.7812	290
4	206	5.6090	2.2952	314	64.4304	521
5	120	4.6983	2.2599	192	37.8252	262
6	270	6.0922	2.2243	396	82.8339	755
7	206	5.6090	2.2951	314	64.4304	521
8	120	4.6983	2.2599	192	37.8252	262
9	162	5.2363	2.2427	252	50.7812	390
10	215	5.7363	2.2007	323	66.4610	571
11	117	4.6983	2.3198	186	37.2474	245
12	156	5.2363	2.3303	240	49.7028	353
13	197	5.6090	2.4023	296	62.8613	464
14	117	4.6983	2.3198	186	37.2374	245
15	258	6.0922	2.3288	372	80.9131	672
16	206	5.7363	2.2978	305	64.9614	511
17	117	4.6983	2.3198	186	37.2374	245
18	156	5.2363	2.3303	240	49.7028	353
19	400	7.1470	2.3239	552	121.8034	1192
20	152	5.1090	2.3956	240	48.4988	337
21	198	5.6470	2.4027	305	62.8411	475
22	246	6.0197	2.4648	372	77.8765	616

Table -3
correlation matrix for inter correlation of molecular descriptors and correlation with the activity.

	$logM_{kid}$	$logM_{liv}$	W	^1X	J	Sz	Log (RB)	W*	Ip_1	Ip_2	Ip_3
$logM_{kid}$	1.0000										
$logM_{liv}$	0.8984	1.0000									
W	-0.7777	-0.6453	1.0000								
^1X	-0.7656	-0.6583	0.9871	1.0000							
J	-0.0298	-0.1196	0.2574	0.3211	1.0000						
Sz	-0.6053	-0.4794	0.9096	0.9183	0.4679	1.0000					
Log (RB)	-0.7731	-0.6480	0.9993	0.9911	0.2899	0.9186	1.0000				
W*	-0.7839	-0.6197	0.9912	0.9640	0.1889	0.8778	0.9869	1.0000			
Ip_1	-0.0086	-0.1477	0.1683	0.1794	0.3119	0.0440	0.1763	0.1660	1.0000		
Ip_2	-0.2007	-0.1203	0.0004	-0.0203	-0.6227	-0.0658	-0.0150	0.0119	-0.5924	1.0000	
Ip_3	-0.5143	-0.3701	0.5825	0.5723	0.5612	0.6498	0.5901	0.5646	-0.1216	-0.3214	1.0000

CONCLUSIONS : -

The objective of present study was to investigate the role of distance- based topological indices in modeling log Mkid and log Mliv i.e. to investigate the role of glycine conjugation. The result have shown that the distance- based topological indices used play positive role in this respect. That is, increase in the magnitude of the distance- based topological indices also increases the rate approaching of Co-A and glycine.

The W and Sz indices in particular accounts for the size, shape and branching and Sz index in addition accounts for the cyclic nature of the compound used. In fact Sz is considered as the modification of W index for cyclic compounds. Thus, all these factors viz. cyclic nature and acyclic branching account for the increase in the glycine conjugation of the benzoic acid used. The result, therefore, indicate that the rate of glycine conjugation of the substituted benzoic acids in the rate liver and kidney mitochondria depends upon size, shape, branching and cyclic nature of the benzoic acid used. Thus the size of the benzoic acid moiety and the bezene ring are the two main parameters, which have dominant effect on the rate of glycine conjugation.

REFERENCES :-

1.Karelson,M., John Wiely & Sons (2000) " Molecular descriptor in QSAR/QSPR " New York.
2.Devillers, J., Balaban, A.T., (Ed), (1999) " Topological Indices and Related Descriptors in QSAR and QSPR" Golden & Breach Science Publisher: Amsterdam. (The Netherland).
3.Diudea, M.V., (Ed), (2000) " QSPR/QSAR Studies by Molecular Descriptors" Babes-Bolyai University, Cluj, Romania.
4.Devillers, J (Ed), "Comparative QSAR" Taylor & Francis (1998) Washington (DC).
5.Sanz, F., Giraldo, J., Manaut F., (Eds.), (1995) " QSAR and Molecular Modling: Concept, Computational Tools and Biological Applications" Prous Science,Barcelona (sp).
6.Hansch, C., Leo, A., (1998) " Exploring QSAR Fundamentals and Applications for Chemistry and Biology" American Chemical Society: Washington (DC).
7.Diudea, M.V., Ivanciuc, O., (1995) "Molecular Topology", Complex, Cluj.
8.Todeschini, R., Consonni, V., (2000) "Handbook of Molecular Descriptors",Wiley-VIH, Weinheim (Ger).
9.Balaban,A.T.,(1982) " Highly discriminating distance-based topological indices", Chem.Phys.Lett., 89,399-404.
10.Balaban, A.T., Basak, S.C., Beteringle, A.,Mills, D., and Supuram , C.T.,(2004) "QSAR study using Toplogical Indices for Inhibition of Carbonic Anhydrase II by sulfanilamide and Schiff's Bases", Mol.Divers.8, 401-412.
11.Khadikar, P.V.,Singh S., Jaiswal, M.,mandloi, D.,(2004), " Topological estimation of electronic absorption bands of arene absoption spectra as tool for modling their toxicity and environmental pollution" Bioorg, Med. Chem. Lett, 14, 4795-4801.
12.Jalali-Haravi, M., Parastar, F., (1999) "Computer modeling of the rate of glycine conjugation with some benzoic acid derivatives: a QSAR study" Quant. Strust. Act. Relat.,18, 134-138.
13.Chaterjee, S., Hadi, A.S., Price, B., (2000) " Regression Analysis by Examples" 3rd Ed. Wiley: New York.
14.Hansch, C., in Correlation Analysis in Chemistry, 397 (Eds. Chapman, N.B. Shorter, J.) Plenum Press, NY, (1978). N. and Smith H. Applied Regression Analysis (J. Wiely and Sons, NY) (1996).
Gern,J.R., Margeriso, D., (1978) " Statistical Treatment of Experimental Data", Physical Sciences Data 2, Elsevier, Amstrdam.