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Topological Modeling of log $D_{7.4}$ of Hydroxylated Aromatic Aldehydes

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Abstract: The quantitative Structure-Aciivity Relationship (QSAR) was performed for a set of 25 hydroxylated aromatic aldehydes for modeling $logD_{7.4}$, responsible for exhibiting toxicity ,using topological indices . The purpose of the study is, therefore, to find out topological dependence of $logD_{7.4}$ vis-à-vis toxicity. Multiple regression analysis (MLR)was used for obtaining statistically significant models. The results show that statistically significant models are obtained in multi-parametric regression model in that Ss,Xu and MSD are found useful in modeling of $logD_{7.4}$.

Keywords: Toxicity , $logD_{7.4}$, topological indices, QSAR, regression analysis.

INTRODUCTION

Of late it has been known[1] that the information about the toxicity of industrial organic chemical to aquatic species can be obtained using molecular descriptors. This is due to fact that such a testing is carried out experimentally, testing provides the most reliable data about the effect of chemicals. However, is time and resource demanding and not deemed suitable for screening of large numbers of potential toxicants. Prediction of toxicity based on QSARs has been thought of as an alternative approach[2].

Aldehydes are important intermediates in production of a variety of industrial processes, such as agrichemicals and pharmaceuticals. In particular, aldehydes are important in the flavour and fragrance industry[3]. Because of their inherent reactivity aldehydes are able to interact with the electron-rich biological macromolecules, in particular protein and nucleic acids and therefore have the potential to cause a number of adverse effects[4] Excess toxicity of aldehydes to fish is thought to be through specific, irreversible, electrophilic mechanisms[5].

Fish acute toxicity studies conducted by McKim *et al*[6] demonstrated that the physiological responses observed in rainbow trout exposed to model aldehydes, including benzaldehyde, is membrane irritation brought on by a concentration response. As direct acting electrophiles aldehydes are also skin-sensitizers[7] and genotoxicants[8].

The octanol – water partition coefficient $logK_{ow,}$ is directly related to the toxicity of aromatic aldehydes. There is 1:1 correlation between toxicity and $logK_{ow}$ .The relationehip is so perfect that in many cases $logK_{ow}$ is considered to represent the toxicity, particularly in those cases where experimental determination of toxicity is next to impossible.However,. In this section,instead of $logK_{ow,}$ we have attempted modeling of $logD_{7.4}$ using topological indices. The purpose of the study is, therefore, to find out topological dependence of $logD_{7.4}$ vis-à-vis toxicity. The most appropriate model will indicate which topological index and or their combination will mimick $logD_{7.4}$.

The partition coefficient is a ratio of concentrations of un-ionlzed compound between the two solutions. To measure the partition coefficient of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is un-ionized. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called log *P*:The distribution coefficient is the ratio of the sum of the concentrations of all forms of the compound (ionized plus un-ionized) in each of the two phases. For measurements of distribution coefficient, the pH of the aqueous phase is buffered to a specific value such that the pH is not significantly perturbed by the introduction of the compound. The logarithm of the ratio of the sum of concentrations of the solute's various forms in one solvent, to the sum of the concentrations of its forms in the other solvent is called Log D .

In addition, log D is pH dependent, hence the one must specify the pH at which the log D was measured. Of particular interest is the log D at pH = 7.4 (the physiological pH of blood serum). For un-ionizable compounds, log P = log D at any pH.

DATASET AND METHODOLOGY USED

The values of **$logD_{7.4}$** of 25 aromatic aldehydes were taken from the work of Schultz and Netzeva[4].Various topological indices were calculated by DRAGON software[9] and structure optimization was done by ACD lab software[10].The names and values of different parameters of compounds are given in Table-1.

MODEL DEVELOPMENT

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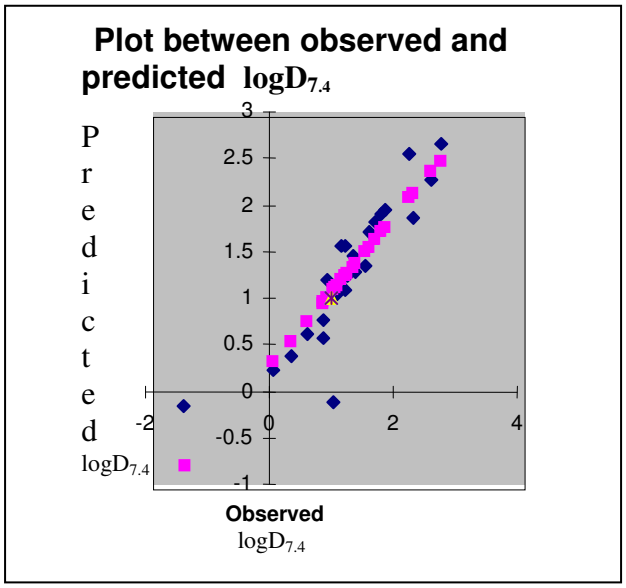
Molecular modeling was carried out by regression analysis in that the method of maximum-R^2 was adopted .The regression analyses were done using Regress-1 program provided by Lukovits , Hungarian Academy of Sciences, Budapest, Hungary and Data analysis program Microsoft 2003. Multiple linear regression analysis was employed in the modeling of **$logD_{7.4}$** .

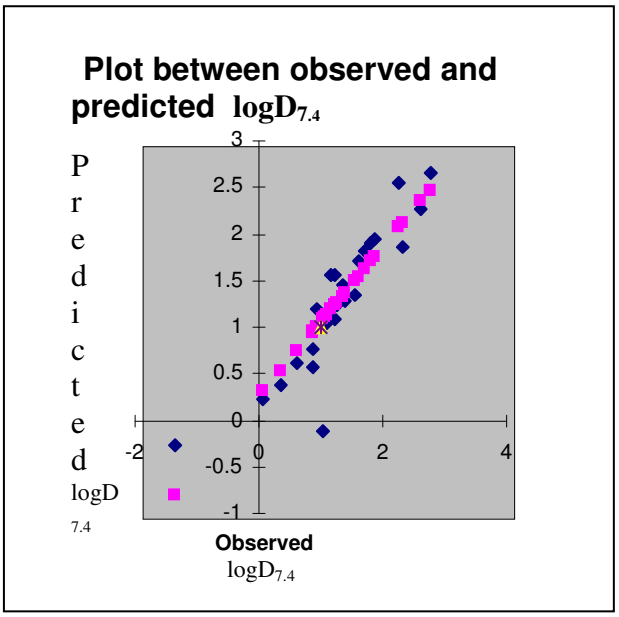
RESULTS AND DISCUSSION

The regression analysis performed by us indicated that there are 10 statistically significant models for modeling $logD_{7.4}$ These models are summarized in Table 2 from this table we observed that statistically significant models are obtained starting from 4–correlating parameters and onward. We observed that models containing 8 and more correlating parameter have the same statistical error. That is they contain one more correlation parameter in that their coefficient are much smaller than their respective standard error. All these models are, therefore, need not to be discussed here. We observed that 7-parametric model is the most appropriate model for modeling $logD_{7.4}$. This model is found as below:

$$\log D_{7.4} = -2.9771 + 0.8953(\pm 0.1781)Ss +$$
$$53.2306(\pm 14.7917)MSD - 0.0806(\pm 0.0551)SMTI$$
$$+ 0.0531(\pm 0.0230)SMTIV + 0.0823(\pm 0.0367)GMTI$$
$$- 0.0217(\pm 0.0075)GMTIV - 5.2778(\pm 1.3696)Xu$$
$$N = 25 R^2 = 0.7967, Se = 0.4567, F = 9.520$$

This model indicates that $logD_{7.4}$ can be modeled using **Ss ,Xu and MSD** topological indices. Increase in value of Ss and MSD and decrease in the value of Xu will favor $logD_{7.4}$





CONCLUSION

The above graph shows close resemblance between observed and predicted values of **$logD_{7.4}$.** Thus **$logD_{7.4}$** can be modeled using **Ss ,Xu and MSD** topological indices. This method is cheaper than experimental determination .It doesn't needs animals and chemicals ,therefore does not pollute the environment.

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Table-1 The names of Hydroxylated aromatic aldehydes and value of different Topological indices

S.No	Name of the compounds	log $D_{7.4}$	Ss	MSD	SMTI	SMTIV	GMTI	GMTIV	Xu
1	**2,3-DihydroxybenzaldehName yde**	1.25	32	0.29	468	1098	388	1886	9.742
2	**2,5-Dihydroxybenzaldehyde**	1.1	32	0.297	476	1122	396	1958	9.796
3	**3,4-Dihydroxybenzaldehyde**	0.92	32	0.305	484	1142	404	2006	9.855
4	**3,4,5-Trihydroxybenzaldehyde**	0.61	37.67	0.283	601	1481	501	2751	10.772
5	**2,3,4-Trihydroxybenzaldehyde**	0.86	37.67	0.279	593	1459	493	2691	10.729
6	**2,4,6-Trihydroxybenzaldehyde**	0.88	37.67	0.278	593	1461	493	2703	10.727
7	**2,4-Dihydroxybenzaldehyde**	1.08	32	0.301	480	1132	400	1982	9.83
8	**3-Ethoxy-2-hydroxycarboxaldehyde**	1.88	33	0.291	794	1604	682	2484	12.02
9	**3-Methoxysalicylaldehyde**	-1.34	31.5	0.281	609	1323	513	2143	10.849
10	**3,5-Dibromosalicylaldehyde**	2.62	31.17	0.278	593	1108	493	1493.9	10.722
11	**4,6-Dimethoxy-2-hydroxybenzaldehyde**	1.22	36.67	0.27	941	2025	803	3365	12.843
12	**2-Hydroxy-3-nitrocarboxaldehyde**	0.06	42	0.275	758	1934	642	3734	11.814
13	**2-Chloro-4-hydroxy-carboxaldehyde**	1.72	30.11	0.301	480	998	400	1542.9	9.83
14	**4-Hydroxy-3-nitrobenzaldehyde**	0.34	42	0.282	774	1978	658	3834	11.89
15	**4-Hydroxybenzaldehyde**	1.22	26.33	0.331	381	849	319	1393	8.909
16	**2-Hydroxy-1-naphthaldehyde**	2.78	33.67	0.254	984	1864	932	3102	12.693
17	**5-Bromovanillin**	1.34	33.92	0.277	760	1548	642	2396.3	11.825
18	**4-Hydroxy-1-naphthaldehyde**	1.81	33.67	0.254	984	1870	928	3138	12.686
19	**5-Bromosalicylaldehyde**	2.33	28.75	0.297	476	960	396	1389.1	9.796
20	**5-Chlorosalicylaldehyde**	2.27	30.11	0.297	476	975	396	1451.3	9.796
21	**2-Hydroxybenzaldehyde**	1.54	26.33	0.309	365	805	303	1273	8.773
22	**3-Bromo-4-hydroxybenzaldehyde**	1.4	28.75	0.305	484	989	404	1494	9.855
23	**3-Methoxy-4-hydroxybenzaldehyde**	1.04	31.5	0.297	625	1367	529	2263	10.937
\24	**3,5-Dibromo-4-hydroxybenzaldehyde**	1.17	31.17	0.283	601	1137	501	1598.8	10.772
25	**3-Ethoxy-4-hydroxybenzaldehyde**	1.6	33	0.298	810	1648	698	2604	12.088

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Table-2 Modeling of $logD_{7.4}$ for Aquatic Toxicity of 25 Hydroxyiated Aromatic Aldehydes using Topological descriptors

Model. No	.Parameters	S.e.	R^2	Adjusted R^2	F
1	Ms	0.7515	0.2556	0.2233	7.8984
2	ZM1V,SMTIV.	0.6423	0.4799	0.4326	10.149
3	Ms, ZM1V,SMTIV.	0.5911	0.5795	0.5194	9.645
4	Ms,ZM1V,ZM2, SMTIV	0.6055	0.5797	0.4956	6.896
5	Ss,MSD,SMTI, GMTIV,Xu	0.4953	0.7328	0.6625	10.423
6	Ss,ZM2V,MSD,SMTI,GMTIV,Xu	0.4933	0.7489	0.6652	8.949
7	Ss,MSD,SMTI,SMTIVGMTI,GMTIV,Xu	0.4567	0.7967	0.7131	9.520
8	Ss,ZM1,MSD,SMTI, SMTIV,GMTI, GMTIV,Xu	0.4481	0.8159	0.7239	8.864
9	Ss,ZM1,ZM2,MSD, SMTI,SMTIV, GMTIV, Xu,SPI	0.4429	0.8314	0.7302	8.217
10	Ss,ZM1,ZM1V,ZM2,MSD,SMTI,SMTIV, GMTIV, Xu,SPI.	0.4547	0.8341	0.7156	7.040

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