IJPSR (2013), Vol. 4, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 March, 2013; received in revised form, 28 May, 2013; accepted, 24 June, 2013

QSAR STUDIES ON POLYCHLORINATED AROMATIC COMPOUNDS USING TOPOLOGICAL DESCRIPTORS

Kumar Nandan*[1], Kumar Ranjan [3], Md. Belal Ahmad [1] and Baidyanath Sah [2]

Department of Chemistry [1], Department of Mathematics [2], T.N.B. College, T.M. Bhagalpur University, Bhagalpur-812 007, Bihar, India
Department of Chemistry, BUIT, Barkatullah University [3], Bhopal, Madhya Pradesh, India

Keywords:

QSAR, QSTR, PCDD, PCDF, MFA, EC_{50} toxicity

Correspondence to Author:

Kumar Nandan

Department of Chemistry, T.N.B. College, T.M. Bhagalpur University, Bhagalpur-812 007, Bihar, India

E-mail: kumarnandan.2008@rediffmail.com

ABSTRACT: Polychlorinated dibenzo-p-dioxins(PCDDs) and Polychlorinated dibenzofurans (PCDFs) represent a large group of industrial and byproduct compound is resistance to chemical and biological degradation and highly toxic.A series of 18 PCDD and PCDF compounds is subjected to QSTR studies by using differnt molecular descripters. The dependent variable used in this study represents log (EC_{50}) values (EC_{50}-median effective concentration during a bioassay). The regression analysis of the data has shown that the toxicity of the compound can be modeled excellently in multi-parametric model.Its resulting model exhibited good R^2 value up to 0.8938. The present work contribute in the identification of those compounds which are very toxic and polluting our environment.

INTRODUCTION: QSTR and QSAR studies have often been carried out by using regression analysis the biological toxicity are being modeled using a set of molecular descriptor. In an earlier, report by Mihaela Caprioara and Mircea V Diudea [1] a QSAR studies on a group of some polychlorinated aromatic compounds.

The introduction of chlorine in PCDD and PCDF gives rise to the more potent pharmacophore.Due to their lipophlic nature PCDD and PCDF concentrate in adipose and hepatic tissues and can persist in an individual for extended lengths of time. With heavier congeners,it may stay with an individual for decades because they are resistant to thermal,metabolic and environmental breakdown.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(7).1000-03

Article can be accessed online on: www.ijpsr.com

These are persistant organic polutants(POPs) that can enter water bodies and eventually sink into the sediment through various transporation routes.These POPs havebeen of a great concern due to their elevated concentrations and wide distribution;they pose not only an environmentel risk through accumulation in human tissues and fluids [2-5].

QSAR can fill the data gap of organic pollutants,decreasses experimental expenses and,in particular,reduce animal testing. They have been widely used in research on the acute toxicity [6], mixture toxicity [7], endocrine disrupting activities [8, 9] and photoinduced toxicity of organic compounds.

In QSAR, we seek to uncover correlations of biological activity with molecular structure with Quantative structure activity relationship (QSPR); we extend the same notion to general chemical property predication and just biological activity. In either case, the relationship is most often expressed by a linear equation that related molecular properties, X, Y .....to the desired activity A_i for compounds i.

$$A_i = mx_i + ny_i + oz_i + b$$

Where m, n and o are the linear slopes that express the correlation of the particular molecular property with the activity of the compound and b is a constant. If only one molecular property is important, for example molecular volume, than above eqn. reduces to the simple form of a straight line, $A_i = mx_i + b$. The slopes and the constant are often calculated using multiple linear regression (MLR) which is analogous with regular linear regression when there is just one independent variable. In constructing graph theoretical schemes to traditional QSAR methods [10] the graph theoretical approach involves (a rather small set of) structural or graph invariants.

In QSTR, one uses statistical methods in order to select critical descriptors and demonstrate a structure – toxicity correlation. In graph theory, one manipulates a structure algebraically, using partial order and ranking based on selected standards of course, graph theoretical descriptors also yield structure property or structure activity correlations.

The authors have developed a QSTR models to predict toxicity of some PCDD and PCDF derivatives. The negative logarithm of EC_{50} ($\log EC_{50}$) was used as the biological activity in QSAR studies.

MATERIAL AND METHODS:

Methodology: This methodology used is to transform the chemical structure in to its molecular graph. This can be done by depleting all the Carbon-hydrogen atom as well as hetro atom hydrogen bonds of chemical structure. In the present investigation, initially, we have used a set of distance based topological indices and physico-chemical parameter.

Statistical Analysis: Based on our earlier studies we have used the Correlation and Rregression Analysis [11-12].

1. **Correlation Analysis:** Correlation analysis of biological activity, topological indices and physicochemical parameter was carried out- Inter-Correlated parameter were eliminated stepwise depending on their individual correlation with the biological activity. All possible combinations of parameters were considered for multiple regression analysis.
2. **Regression Analysis:** Multiple regression analysis a programmed carried out by 'Multi Regress' using stepwise regression methodology carried out. It was carried out using a computer program, graph pad and NCSS software, In order to obtain appropriate models; we used the maximum R^2 Method. In addition we also calculation the quality factor Q, as the ratio of correlation coefficient (R) and the standard error of estimation (Se) i.e. Q= R/Se. Finally, the cross-validation method was used to establish the predictive potential of our models.

Molecular Descriptors: The topological parameter Winner indices(W) and Balban indices(J) in MFA-QSAR equation specify the regions of different compounds in the training set, leading to either an increase or decrease in activities [13].

1. **Winner indices (W):** Winner is defined as the sum over all bonds of the product of the number of vertices on each side of the bond. Mathematically, W index is defined as:

$$W = W(G) = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} d\,i\,j$$

Where d_{ij} is the shortest distance between two vertices (atoms) s and j

2. **Balban indices (J):** The Balban index J is defined by;

$$J = J(G) \quad \sum_{\mu+1}^{M} d_i\, d_j$$

Where M is the number of bonds in a graph G and μ is the cyclomatic number of G.

3. **Physico-Chemical Parameters:** We have used Chemsketch program of ACD lab 27 for the calculation of Physico-chemical parameters. These parameter used in present work includes molecular weight (MW), Molecular refraction (MR), Molecular volume (MV), Parachor (P_r) Surface Tension (γ), Density (d), Index of Refraction (η), Polarizability (α). Attempt has also been mode to combine the physicochemical with distance based topological indices with a hope of obtaining models with better statistics

Software: Allmolecular modeling studies were carried out using HYPERCHEM(version 7.5) and DRAGON software. The structures of molecules were drawn using Chemsketch software. NCSS Inc. is a leading worldwide provider of predictive analytics software and solutions.

RESULT AND DISCUSSION: The basic PCDD and PCDF pharmacophore used in the present studies is shown in **table 1**.

TABLE 1: STRUCTURE OF COMPOUNDS ACTIVITY AND THEIR MOLECULAR DESCRIPTORS

Compounds	log(EC_{50})	β	α	W	*J*
2,3,4,6,7,8-Hexachloro-dibenzofuran	-8.33	87.77	31.53	616	1.849
1,2,3,4,7,8-Hexachloro-dibenzofuran	-7.64	87.77	31.53	612	1.864
1,2,3,6,7,8-Hexachloro-dibenzofuran	-7.57	87.77	31.53	613	1.859
2,3,4,7,9-pentachloro-dibenzofuran	-7.7	83.06	29.6	532	1.837
2,3,4-trichloro-dibenzofuran	-5.72	73.63	25.74	385	1.81
2,3-dichloro-dibenzofuran	-6.33	68.91	23.81	330	1.755
2,6-dichloro-dibenzofuran	-4.61	68.91	23.81	327	1.775
2-chloro-dibenzofuran	-4.55	64.19	21.89	272	1.751
4-chloro-dibenzofuran	-4.5	64.19	21.89	267	1.786
1-chloro-dibenzodioxin	-5	66.64	22.52	334	1.714
2,8-chloro-dibenzodioxin	-6.49	71.36	24.45	413	1.667
2,3,7-trichloro-dibenzodioxin	-8.15	76.07	26.38	488	1.678
1,3,7,8-tetrachloro-dibenzodioxin	-7.1	80.79	28.31	562	1.717
2,3,7,8-tetrachloro-dibenzodioxin	-9	80.79	28.31	571	1.688
1,2,3,4,7-chloro-dibenzodioxin	-6.19	85.5	30.23	632	1.786
1,2,3,4,7,8-hexachloro-dibenzodioxin	-7.55	90.22	32.16	730	1.79
1,2,3,7,8-pentachloro-dibenzodioxin	-8.1	85.5	30.23	648	1.738
octachloro-dibenzodioxin	-0.6	99.65	36.02	915	1.878

β= Refractivity; α = Plorizability; W= Winner indices; *J*= Balban

The correlation matrix as recorded in **table 2** is important in the sense that it represents inter relationship between the observed value of the variable on one side and its estimated value expressed in terms of the dependent variables on the other. These tables show that multiparametric model involving pair is good.

TABLE 2: CORRELATION MATRIX FOR THE INTER-CORRELATION OF STRUCTURE DESCRIPTORS AND THEIR CORRELATION WITH THE ACTIVITY

	log(EC_{50})	*β*	*α*	*W*	*J*
log(EC_{50})	1.00000				
β	-0.61961	1.00000			
α	-0.61489	0.999043	1.00000		
W	0.009082	0.551013	0.58226	1.00000	
j	-0.58707	0.981806	0.973574	0.432555	1.00000

TABLE 3: RESULT OF PROPOSED MODELS USING MAXIMUM – R^2 METHOD

Model	Parameters	S_e	R	R^2	F	R_A^2	Q
1	α, β, J	0.5759	0.9295	0.8640	29.6477	0.8349	1.6139
2	α, W, J	0.5395	0.9384	0.8806	34.4334	0.8551	1.7393

We have carried out stepwise multiple regression analysis for modeling of Compound no 18. The results of regression analysis are presented in **table 3** which shows possible correlation equation.

Final equation;

$$-1.618(\pm 0.225)\alpha + 26.940(\pm 3.518)J + 0.02800(\pm 0.0047)W - 23.945$$

The numbers accompanying descriptors in the equation represent their positions in three-dimensional MFA grid. We have carried out step wise multiple regression analysis for modeling of compound no. 18.

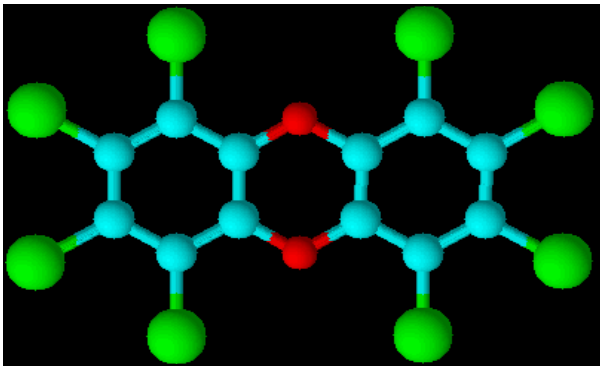

FIG. 1: ALIGNMENT OF THE COMPOUNDS 18 USED IN THE TRAINING SET OF QSAR ANALYSIS

In order to confirm the above-mentioned finding we have estimated Q-value and observed that it is highest for model. At this stage, It is interesting to comments an adjustable R^2 (R_A^2) Coefficients. It takes into accounts of adjustment of R^2 therefore If a variable is added that does not contribute its fair share, the R_A^2 will actually decline. If R_A^2 always increases then an independent variable is added. On other side R_A^2 will decreases, this means the added variable does not reduce the unexplained variation enough to offset the loss of degrees of freedom. In our case, R_A^2 value increases with increasing number of parameters. This indicates that the new parameters have a fair share in the proposed model. Further support in out favors in obtained by estimating EC_{50} and compares the same with observed EC_{50} value. Such a comparison is demonstrated in **table 4**. We observed that the estimated value is very close to the observed values.

TABLE 4: COMPARISONS OF OBSERVED AND ESTIMATED *EC*$_{50}$

Compound No	Compound Activity(EC_{50})	Model 05	
		Estimated	*Residuals*
1	-8.33	-7.90362	-0.42368
2	-7.64	7.61152	-0.02848
3	-7.57	7.71822	0.14821
4	-7.70	-7.45594	-0.24406
5	-5.72	-6.05343	0.33342
6	-6.33	-5.92221	-0.37779
7	-4.61	-5.49741	0.88741
8	-4.55	-4.57724	0.02724
9	-4.50	-3.77434	-0.72596
10	-5.00	-4.85749	-0.14251
11	-6.49	-7.03460	0.54460
12	-8.15	-7.76121	-0.38879
13	-7.10	-7.76150	0.66149
14	-9.00	-8.29077	-0.70923
15	-6.19	-7.04942	0.85941
16	-7.55	-7.32064	-0.22936
17	-8.10	-7.89455	-0.20545
18	-6.00	-6.01591	0.01590

The most active molecule no-18 was used for MFA model. A common substructure-based alignment was adopted in the present study, which attempted to align molecules to the template molecule on a common backbone. Finally, we have plotted a graph between observed and calculated value, which yielded predictive correlation co-efficient.

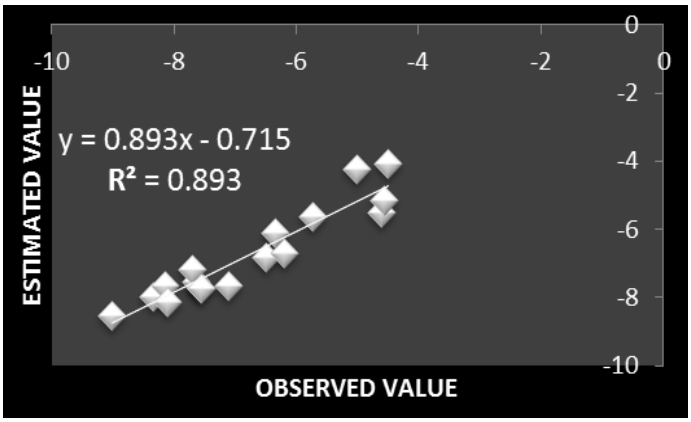

FIG. 2: PLOT OF OBSERVED VS. ESTIMATED ACTIVITY EC_{50}

CONCLUSION: On the basis of above observation it leads to the conclusion that the activity logEC_{50} of the present set of compounds can be successfully modelled using molecular descriptors. It was also observed that out of the molecular descriptors used α, β, W and *J* are most useful for this purpose. The MFA equation suggested that (-ve) sign of α descriptor is disfavour the activity while (+Ve) sign of W and *J* parameters indicated that they favored activity.

QSAR for regulatory purpose should be defined domain of applicability appropriate measure of goodness-of-fit, robustness and predictive power. Our results open very interesting perspectives regarding polychlorinated aromatic compounds with toxicity.

ACKNOWLEDGEMENTS: One the author (Kumar Nandan) is highly obliged and thankful Dr. Sunita Gupta, dept. of chemistry, A.P.S. University Rewa, India, for introducing him to the fascinating field of Chemical Topology, Graph Theory and statistical work.

REFERENCE:

1. Mihaela caprioara and Mircea V Diudea. *Indian J. of Chemistry*. 2003, 42A, 1368-1378
2. M. Athanasiadou, S.N. Cuadra, G. Marsh, A. Bergman, and K. Jakobsson, Polybrominated diphenyl ethers (PBDEs) and bioaccumulative hydroxylated PBDE metabolites in young humans from Managua, Nicaragua, Environ. Health Perspect. 2008, 116, 400–408.
3. S. Khan, Q. Cao, A.J. Lin, and Y.G. Zhu, Concentrations and bioaccessibility of polycyclic aromatic hydrocarbons in wastewater-irrigated soil using in vitro gastrointestinal test, Environ. Sci. Pollut. Res. 2008, 15, 344–353.
4. H. Iwata, M. Watanabe, Y. Okajima, S. Tanabe, M. Amano, N. Miyazaki, and E.A. Petrov, Toxicokinetics of PCDD, PCDF, and coplanar PCB congeners in Baikal seals, Pusa sibirica: Agerelated accumulation, maternal transfer, and hepatic sequestration, Environ. Sci. Technol. 2004, 38, 3505–3513.
5. P.M. Hoai, N.T. Ngoc, N.H. Minh, P.H. Viet, M. Berg, A.C. Alder, and W. Giger, Recent levels of organochlorine pesticides and polychlorinated biphenyls in sediments of the sewer system in Hanoi, Vietnam, Environ. Pollut. 2010, 158, 913–920
6. X. Li, T.A. Zhang, X.M. Min, and P. Liu, Toxicity of aromatic compounds to Tetrahymena estimated by microcalorimetry and QSAR, *Aquat. Toxicol.* 2010, 98 322–327.
7. J. Neuwoehner, T. Zilberman, K. Fenner, and B.I. Escher, QSAR-analysis and mixture toxicity as diagnostic tools: Influence of degradation on the toxicity and mode of action of diuron in algae and daphnids, *Aquat. Toxicol*. 2010, 97 58–67.
8. F. Li, Q. Xie, X.H. Li, N. Li, P. Chi, J.W. Chen, Z.J. Wang, and C. Hao, Hormone activity of hydroxylated poly brominated diphenyl ethers on human thyroid receptor-beta: In vitro and in silico investigations, *Environ. Health Perspect*. 2010, 118 602–606.
9. F. Li, X.H. Li, J.P. Shao, P. Chi, J.W. Chen, and Z.J. Wang, Estrogenic activity of anthraquinone derivatives: In vitro and *in silico* studies, *Chem. Res. Toxicol*. 2010, 23 1349–1355.
10. V.K. Arawal, S.Srivastava, P.V. Khadikar and C.T. Supuran, QSAR study on Sulfanilamide Schiffs Base: Carbonic Anhydrase (CA) Inhibitors, *Bioorganic & Medicinal Chemistry*, 2003 , 11, 5353-5362
11. Kumar Nandan,Baidyanath Prasad,Sunita Gupta and Kumar Ranjan,Statistical Significance of Phthalimide Derivatives,Indian J. Mathematics & Mathematical Science, 2011, 7, 51-62
12. Shalini Singh, QSAR study on the inhibition of the human carbonic anhydrase cytosolic isozyme hCA VII†,J. Indian Chem. soc. 2013,90, 245-252
13. V.K. Arawal, Jyoti Singh,K.C. Mishra, P.V. Khadikar and Yusuf Ali Jaliwala,QSAR Studies on the use of 5,6-dihydro-2-pyrones as HIV-1 protease inhibitors,Arkivoc 2006 ( ), 162-177

How to cite this article:
Nandan K, Ranjan K, Ahmad MB and Sah B: QSAR studies on Polychlorinated Aromatic compounds using Topological descriptors. *Int J Pharm Sci Res* 2013: 4(7); 2691-2695. doi: 10.13040/IJPSR. 0975-8232.4(7).2691-95