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QSTR Analysis of Phenol Derivatives with the help of Topological parameter

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Abstract: In this article, a Quantitative structure Toxicity Relationships (QSTR) of twenty five phenol derivatives is presented. The QSTR study is mainly based on topological parameter. The topological parameter has been evaluated by CAChe prosoftware. The calculations of topological parameters have been done by MOPAC 2007. The statistical parameter has been calculated by SSP software. Various QSTR models are developed but best four models are reported on the basis of cross validation and correlation coefficient. Out of above four models, Model no. 4 is the best model, which is selected by on the basis of SE, SEE, t-valve, p-value and degree of freedom. Model no. 4 is evaluated by shape index first order and connectivity index second order. So we can say that the shape index first order and connectivity index second order are the better describe for the required maximal inhibitory concentration to new phenol derivative.

Key word: Phenol, Topological parameter, Shape index, Connectivity index.

Introduction:

Phenol was widely used as an antiseptic, especially as Carbolic soap, from the early 1900s through the 1970s. Phenol and its vapors are corrosive to the eyes, the skin, and the respiratory tract.[1] Repeated or prolonged skin contact with phenol may cause dermatitis, or even second and third-degree burns due to phenol's caustic and defatting properties.[2] Inhalation of phenol vapor may cause lung edema. The substance may cause harmful effects on the central nervous system and heart, resulting in dysrhythmia, seizures, and coma.[3] The kidneys may be affected as well. Exposure may result in death and the effects may be delayed. Long-term or repeated exposure of the substance may have harmful effects on the liver and kidneys."[4] There is no evidence to believe that phenol causes cancer in humans.[5] Besides its hydrophobic effects, another mechanism for the toxicity of phenol may be the formation of phenoxyl radicals.[6]The synthesis of novel pharmacologically active molecules with reduced toxicity is of prime interest. Recently, QSAR has gained importance in the field of pharmacological sciences [7]. Quantitative structures Activity Relationships (QSAR) are predictive tools for a preliminary evaluation of the activity of chemical compounds by using computer-aided models. The Hohenberg and Khontheorm based DFT[8-10] provide a major boost to the computational chemistry .The performance of DFT method in description of structural, energetic and magnetic molecular properties has been reviewed quite substantially in recent time. DFT methods are in general capable of generating a variety of isolated molecular properties [11-18]. Quantitative structure–activity relationship (QSAR) techniques increase the probability of success and reduce time and cost involvement in drug discovery process [19-20]. Earlier, we have published Quantum Chemical Parameter is a predictive tool of maximal inhibitory concentration of twenty five phenol derivatives [21]. In this article, a Quantitative structure Toxicity Relationships (QSTR) of next twenty five phenol derivatives is presented. The QSTR study is mainly based on topological parameter. The topological parameters have been evaluated by CAChe prosoftware . The calculations of topological parameters have been done by MOPAC 2007. The statistical parameter has been calculated by SSP software.

Experimental:

For QSTR study of phenol derivatives, it is necessary to identify a good tool. Following topological descriptors have been used for this study. The evolution of topological descriptor is given below:

Kier & Hall molecular connectivity index (χ) (22-29)

This index, originally defined by Randic´ (1975), and as subsequently refined by Kier and Hall (1976) is a series of numbers designated by "order" and "subgraph type." There are four subgraph types: Path, Cluster, Path/Cluster, and Chain. These types emphasize different aspects of atom connectivity within a molecule; the amount of branching ring structures present and flexibility. Here we refer to these subgraph types as P, C, PC, and CH, respectively.

Molecular connectivity index of order n corresponding to subgraphtype s isdenoted by ${}^{n}\chi_{s}$.Given an order n and a subgraphtype s, one considers all connected subgraphs of type s consisting of n edges. For each vertex v_i in a subgraph, itsvalence δv_i (with respect to the entire graph) is calculated and the partial index ${}^{n}P$ corresponding to the given subgraph is found according to:

$$ {}^{n}P(subgraph) = \prod_{i=1}^{n} 1/\sqrt{\delta_{v_i}} $$

(*n* = number of subgraph vertices).

Finally, the partial indices are summed over all connected subgraphs of the requested type s (Kier and Hall 1976, 1985):

$$ {}^{n}\chi_{s} = \sum {}^{n}P(subgraph) $$

Order zero χ indices, CHI-0

Let us consider the order zero χ indices first, in the first column (CHI-0), which represent the simplest subdivision or subgraph: the set of vertices. The number of subgraphs of order zero is therefore equal to the number of skeletal atoms or vertices. Each vertex has a property δ, which is the number of its electrons in sigma bonds to skeletal neighbors.

$$ \delta = \sigma - h $$

Where:

σ= number of electrons in σbonds to all neighbors.
h = number of H atoms bonded to atom *i*.

The zerothorder subgraph connectivity weight assigned to each vertex is:

$$ c = \delta^{-1/2} $$

The order zero χ index is the sum of all vertex weights in the graph, that is, over all atoms in the skeleton.

$$^{0}\chi = \sum_{i=1}^{\text{Number of atoms}} c_i$$

The zero order χindex holds little structural information. Only the presence of the nearest neighbor to each atom is captured. In the series methane through tetra fluoro methane, we see an increase in CHI-0, which reflects the increasing size of the molecule skeleton.

Kier's shape indices {κn (n = 1, 2, 3)} (22-29)

These indices compare the molecule graph with "minimal" and "maximal" graphs, where the meaning of "minimal" and "maximal" depends on the order n. This is intended to capture different aspects of the molecular shape.

Order 1:

The descriptor κ_1 encodes the count of atoms and the presence of cycles relative to the minimal and maximal graphs. For N vertices, the maximal graph includes edges between allvertex pairs. For the minimal graph a linear path of N - 1 edges connecting the vertices is taken.

The shape index of order 1 is then defined as:

$$\kappa_1 = 2P_{min}P_{max}/P^2$$

where*P* is the number of edges in the graph (edges are paths of length 1, hence the subscript on the κ_1), Pmax is the number of edges in the maximal graph -- namely N(N - 1)/2 -- and Pmin is the number of edges in the minimal graph -- namely N - 1.

By inserting the formulas for Pmax and Pmin, one obtains the implemented formula:

$$\kappa_1 = N(N-1)^2/P^2 \qquad (1)$$

Order 2:

The descriptor κ_2 encodes the branching. P, Pmin, and Pmax now denote the number of paths of length 2 in the corresponding graphs. The maximal graph is taken to be the star graph in which all atoms are adjacent to a common atom. Thus, Pmax = (N - 1) (N - 2)/2. The linear graph is again taken as the minimal graph, so Pmin = N - 2. Equation (1) thus yields:

$$\kappa_2 = (N-1)(N-2)^2/P^2 \qquad (2)$$

Order 3:

For order 3, the counts of paths of length 3 are considered, and the maximal graph chosen is a twin-star (Kier 1990) with Pmax = (N - 1) (N - 3)/4 for N odd and Pmax = $(N - 2)^2/4$ for N even. The minimal graph is again the linear one with Pmin = N - 3.

The equation is adjusted by another factor of 2 -- in the words of the index designer -- "to bring the values into rough equivalence with the other kappa values" (Kier 1990, Hall and Kier 1991):

$$\kappa_3 = (N-1)(N-3)^2/P^2 \quad \text{for } N \text{ odd}$$

$$\kappa_3 = (N-3)(N-2)^2/P^2 \quad \text{for } N \text{ even} \qquad (3)$$

Solvent Accessible surface area

The solvent accessible surface area (SASA) is the surface area of a bio molecule (protein, DNA, etc.) that is accessible to a solvent. Is usually quoted in angstrom square (a standard unit of measurement in molecular biology).SASA was first described by Lee & Richards in 1971 is sometimes called the Lee-Richards molecular surface.

Molar refractivity

The molar refractivity is a constitutive-additive property that is calculated by the Lorenz-Lorentz formula:

$$MR = \frac{n^2 - 1}{n^2 + 2} * \frac{M}{\rho} \qquad (4)$$

Where *M* is the molecular weight, *n* it is the refraction index and *r* the density, and its value depends only of the wave longitude of the light used to measure the refraction index..

Result and Discussion:

Twenty five phenol derivatives have been chosen with their toxicity values **[30]** in terms of IC50 against tetrahymenapyriformis are placed in Table 1. Experimental determination of toxicological and biochemical end points as well as the human health end points is a difficult task. Hence QSTR modeling of the toxicity of compounds on tetrahymenapyriformis is vital importance in investigating its toxicity in terms of its (50%) inhibitory concentration. The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a compound in inhibiting biological or biochemical function. This quantitative measure indicates how much of a particular drug or other substance (inhibitor) is needed to inhibit a given biological process (or component of a process, i.e. an enzyme, cell, cell receptor or microorganism) by half. In other words, it is the half maximal (50%) inhibitory concentration (IC) of a substance (50% IC, or IC_{50}). In this paper, we have done quantitative structure toxicity relationship analysis of twenty five phenol derivatives with the help of topological parameter. The values of descriptor are included into Table 2. Various QSTR models are developed but best four models are reported on the basis of cross validation and correlation coefficient.

PT^1=0.599147χ1-15.9199MR +5.75132χ2-6.99964
r^{CV2}=0.232431
r^2=0.69058
PT^2=0.379271κ1+1.2985χ1-1.5968 κ2-13.7201
r^{CV2}=0.526529
r^2=0.655615
PT^3=-0.00828465S_AS_A+1.39794κ2-13.8948
r^{CV2}=0.536892
r^2=0.592876
PT^4=0.681026κ1-0.896055χ2-10.1498
r^{CV2}=0.414939
r^2=0.734684

Table 1. Twenty five Phenol derivatives with observed toxicity against *Tetrahymena pyriformis*

S.No.	Compound	Toxicity
1	2,5-Dichlorophenol	1.128
2	2,3-Dichlorophenol	1.271
3	4-Chloro-2-methylphenol	0.700
4	4-Chloro-3-methylphenol	0.795
5	2,4-Dichlorophenol	1.036
6	3-ter.butylphenol	0.730
7	4-ter.butylphenol	0.913
8	3,5-Dichlorophenol	1.562
9	2-Phenylphenol	1.094
10	2,4-Dibromophenol	1.403
11	2,4,6-Trimethylphenol	0.418
12	3,4,5-Trimethylphenol	0.930
13	2,4,6-Trimethylphenol	1.695
14	4-Chloro-3,5-dimethylphenol	1.203
15	4- Bromo-2,6-dichlorophenol	1.779
16	2,4,5-Trichlorophenol	2.100
17	4-Bromo-6-chloro-2-methylphenol	1.277
18	4-Bromo-2,6-dimethylphenol	1.278
19	2,4,6-Tribromophenol	2.050
20	2-ter.butyl-4-methylphenol	1.297
21	4-Chloro-2-isopropyl-5-methylphenol	1.862
22	6-ter.butyl-2,4-dimethylphenol	1.245
23	2,6-Dimethylphenol	2.113
24	2,4-Dibromo-6-phenylphenol	2.207
25	2,6-Di-ter.butyl-4-methylphenol	1.788

Table 2. Values of topological descriptor of Twenty five Phenol derivatives

C.N.	$\chi 1$	$\chi 2$	M_R	κ^1	κ^2	S_AS_A	Toxicity
1	6.853	4.198	37.362	7.111	2.722	136.86	1.128
2	6.853	4.215	37.362	7.111	2.722	118.16	1.271
3	6.853	4.198	37.598	7.111	2.722	118.62	0.7
4	6.853	4.198	37.598	7.111	2.722	118.89	0.795
5	6.853	4.198	37.362	7.111	2.722	115.72	1.036
6	8.483	4.999	46.418	9.091	3.164	134.46	0.73
7	8.483	4.999	46.418	9.091	3.164	136.65	0.913
8	6.853	4.182	37.362	7.111	2.722	136.15	1.562
9	9.096	6.377	52.888	9.551	4.481	117.58	1.094
10	6.853	4.198	42.998	7.111	2.722	132.06	1.094
11	7.724	4.626	42.876	8.1	2.939	117.48	1.403
12	7.724	4.609	42.876	8.1	2.939	118.15	0.418
13	7.724	4.609	42.876	8.1	2.939	116.05	0.93
14	7.724	4.609	42.639	8.1	2.939	129.07	1.695
15	7.724	4.609	44.985	8.1	2.939	129.33	0.017
16	7.724	4.609	42.166	8.1	2.939	128.3	2.1
17	7.724	4.609	45.221	8.1	2.939	129.78	1.277
18	7.724	4.609	45.457	8.1	2.939	116.3	1.278
19	7.724	4.609	50.621	8.1	2.939	119.23	2.05
20	9.353	5.41	51.459	10.083	3.395	118.57	1.297
21	9.301	5.52	51.789	10.083	3.806	114.31	1.862
22	10.224	5.82	56.5	11.077	3.63	117.4	1.245
23	6.853	4.215	37.835	7.112	2.722	121.36	2.113
24	10.836	7.182	68.134	11.484	4.888	121.15	2.207
25	12.724	7.032	70.125	14.063	4.349	131.88	1.788

Table 3. Values of predicted toxicity from P_T^1 to P_T^4

C.N.	P_T^1	P_T^2	P_T^3	P_T^4	Toxicity
1	1.125	1.127	1.126	1.129	1.128
2	1.270	1.274	1.126	1.275	1.271
3	0.4	0.252	0.685	0.823	0.7
4	0.791	0.790	0.685	0.710	0.795
5	1.030	1.123	0.921	1.022	1.036
6	0.70	0.689	0.921	0.72	0.73
7	0.912	0.947	0.921	0.911	0.913
8	1.563	1.056	0.921	1.542	1.562
9	1.093	1.227	0.449	1.129	1.094
10	1.091	0.111	0.921	0.115	1.094
11	1.402	1.127	0.921	1.329	1.403
12	0.419	0.325	0.921	0.421	0.418
13	0.90	0.896	0.921	0.970	0.93
14	1.694	1.082	0.921	1.680	1.695
15	0.016	0.0147	1.362	0.0168	0.017
16	2.2	1.593	2.348	1.983	2.1
17	1.271	1.177	1.598	1.229	1.277
18	1.277	1.127	0.685	1.369	1.278
19	2.03	2.85	1.764	2.058	2.05
20	1.291	1.209	0.449	1.287	1.297
21	1.864	1.95	2.275	1.859	1.862
22	1.243	1.123	1.249	1.234	1.245
23	2.110	1.975	2.445	2.158	2.113
24	2.205	2.348	2.345	2.219	2.207
25	1.785	1.847	2.246	1.787	1.788

Table 4. Statistical summary of best five models

PT	SE	SEE	t-VALUE	p-VALUE	DOF	VU	VC
1	0.0703	0.2036	12.3808	0.0000	0.8639	χ1, MR, χ2	3
2	0.0851	0.2778	8.4653	0.0000	0.7465	κ1, χ1, κ2	3
3	0.1308	0.4186	4.3233	0.0001	0.4243	SASA, κ2	2
4	0.0211	0.0595	45.1899	0.0000	0.9884	κ1, χ2	2

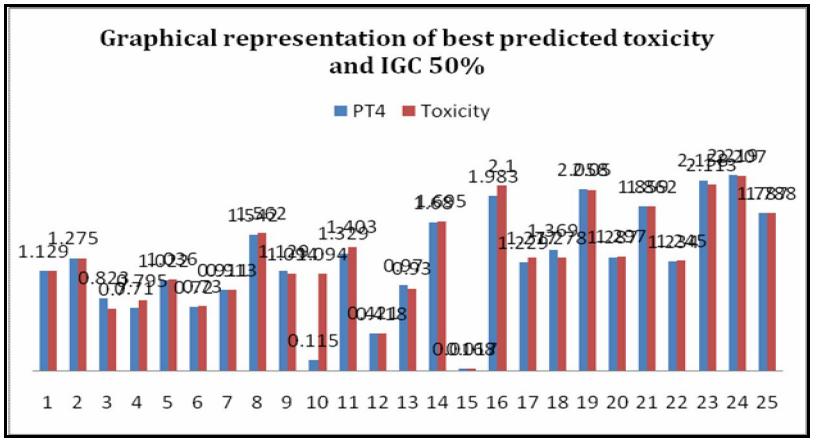

Figure1: Relationship between predicted toxicity and observed toxicity

Out of above four models, Model no. 4 is the best model, which is selected by on the basis of SE, SEE, t-valve, p-value and degree of freedom. Which are placed in table 4. The relationship between IGC50% and PT^4 are presented in Fig.1. Model no. 4 i.e. PT^4 is evaluated by shape index first order and connectivity index second order.

Conclusion:

From the above discussion we can conclude that the shape index first order and connectivity index second order are the better describe for the required maximal inhibitory concentration to new phenol derivative.

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