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Modelling of Parachor of Phenolic Derivatives by Computational Methods

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Abstract
Parachor is a concept used in drug design to describe the physicochemical property of a compound, specifically its ability to balance between polar and non-polar interactions. It is a parameter that combines surface tension and molar volume to quantify how molecules interact with solvents, interfaces, and biological systems. Parachor is often applied to predict how molecules will behave in drug formulation. The paper deals with structure-activity relationships of phenols and its derivatives for the development of predictive models from several descriptors. To developing the models for Parachor of phenol derivatives we used descriptors like Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e, eHOMO, eLUMO and the best model proposed for Parachor of Phenol's & its Derivatives.

Keywords
*Parachor**,** QSAR, Molecular descriptors, 3D MoRSE descriptors, FDI descriptors, RDF descriptors, Moreau autocorrelation descriptors, correlation coefficient, PRESS, SPRESS, PSE, LSE, PE*

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INTRODUCTION

Parachor is an additive constitutive property of a molecule and is related to the molar volume and the surface tension. The parachor of a steroid can be calculated from its constituent atoms and bonds. The parachor of a biologically active molecule is related to the ability of that molecule to permeate hydrophobic regions of cells, especially cellular membranes. An examination of the parachor values of a large number of steroids shows that these values are correlated with a number of different biological activities, from independent sources[1].
Parachor helps in the rational design of drugs by providing insights into solubility, permeability, drug-receptor interactions, and formulation stability, which ultimately contribute to the effectiveness, safety, and overall success of a drug candidate.

Parachor is a scientific quantity defined according to the formula:

$$P = \gamma 1/4 * M / d$$

where $\gamma 1/4$ is the fourth root of surface tension, M is the molar mass, and d is the density.

Parachor "has been used in solving various structural problems[2]. Parachor of phenol derivatives which used in the study are given in **Table (1.1)**.
Parachor has been used extensively in physical organic chemistry for structure determination. It has rarely been used as a parameter for the correlation of structure and biological activity. We have reexamined the parachor concept for structure-activity correlations of some closely related analogs. Parachor is an additive and constitutive molecular parameter consisting of two physical properties, molar volume and surface tension, factors which appear to be important in the passage of a drug or hormone from the site of administration or synthesis to the site of action. Correlations between parachor values and biological activities for a number of drug classes have been examined[3].

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Phenol and its derivatives are known to induce caspase-mediated apoptosis activity and cytotoxicity on various cancer cell lines. Quantitative structure-activity relationship studies on the cellular apoptosis and cytotoxicity of phenolic compounds have been investigated recently by Selassie and colleagues[4] wherein models were developed for various carcinogenic cell lines. Using computational method, we suggest model having best prediction power for parachor. Computational chemistry is applications of computer and computer enable calculations in chemistry for various purposes. One most important scope of computational Chemistry is QSAR and QSPR followed by Drug Designing. QSAR i.e. Quantitative Structure Activity Relationship provides a way to correlate the effect of structure over activity in terms of mathematical descriptors viz. Topological Indices. Quantitative structure-activity relationships (QSAR) represent an attempt to correlate structural or property descriptors of compounds with activities. These physicochemical descriptors, which include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include chemical measurements and biological assays. QSAR currently are being applied in many disciplines, with many pertaining to drug design and environmental risk assessment[5]. The properties of a substance (such as physicochemical reactivity, behavior or biological activity) are ultimately determined by its molecular structure. Quantitative structure-activity relationship (QSAR) and Quantitative structure-property relationship (QSPR) models represent well-established tools for the molecular design of new compound with desired properties[6]

II. Material And Method

Modelling of Parachor of Phenol derivatives we used 3D MoRSE descriptors (3D Molecule Representation of Structures based on Electron diffraction), Folding Degree Index (Φ) FDI, radial distribution function (RDF), Moreau–Broto Autocorrelation Descriptors, GETAWAY Descriptors (R3e (autocorrelation of lag3/weighted by atomic Sanderson electro negativity) Descriptors), Quantum-Chemical Descriptors (eHOMO, eLUMO) Descriptors.

To developing the first model for Total Polar surface area of phenol derivatives in we used eight descriptors Mor29p, Mor20e, Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e. There are 49 observations (molecules) are used to build this model for Total Polar surface area. By regression Statistics we get correlation coefficient is 0.410008, r^2 is 0.168106, Adjusted R Square *is* 0.001728, and Standard Error is 13.52154 for model-I which described by equation 1.

To developing the first model for Parachor of phenol derivatives in we used eight descriptors Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e, eHOMO, eLUMO. There are 49 observations (molecules) are used to built first model for Parachor. By regression Statistics we get correlation coefficient is 0.86, r^2 is 0.7396, Adjusted R Square *is* 0.6875, and Standard Error is 36.557 for model-I which described by equation 1.

Predicted Parachor = (27.79748*Mor04m) + (-220.12*Mor23m) + (-1041.1*FDI) + (6.06875*RDF045m) + (0.848495*MATS5p) + (126.8669*R3e) + (7.308418*eHOMO) + (4.766519*eLUMO) +1165.858……. (1)

Analysis of variance of Model –I for Parachor

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	8	151836	18979	14.201	1.55E-09
Residual	40	53458	1336.4		
Total	48	205293			

To developing the second model for Parachor of phenol derivatives in we used eight descriptors Mor29p, Mor20e, Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e. There are 49 observations (molecules) are used to built this model for Parachor. By regression Statistics we get correlation coefficient is 0.9342, r^2 is 0.8728, Adjusted R Square *is* 0.8474, and Standard Error is 25.549 for model-II which described by equation 2.

Predicted Parachor = (-17.3009*Mor29p) + (105.3335*Mor20e) + (36.43032*Mor04m) + (-72.3426*Mor23m) + (-1401.13*FDI) + (5.990181*RDF045m) + (-2.06621*MATS5p) + (92.71059*R3e) + 1469.727……. (2)

Analysis of variance of Model –II for Parachor

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	8	179183	22398	34.312	1.48E-15
Residual	40	26111	652.77		

Total	48	205293

Table (1.1) Observed and Predicted value of Parachor using Eq. (2)

S. No.	Abbreviations	Parachor ± 4.0cm^3	*Predicted Parachor ± 4.0cm3*	*Residuals*	*Standard Residuals*
1	4MOPH	278.9	289.87	-10.97	-0.47
2	4EOPH	318.7	341.34	-22.64	-0.971
3	4PROPH	358.5	351.35	7.148	0.3065
4	4BOPH	398.3	406.57	-8.273	-0.355
5	4HXOPH	477.8	463.97	13.833	0.5931
6	PH	222.2	235.52	-13.32	-0.571
7	4NPH	277.7	259.86	17.836	0.7647
8	4CLPH	258.1	262.79	-4.694	-0.201
9	4IPH	297.8	314.54	-16.74	-0.718
10	4HOBAL	267.3	245.74	21.564	0.9246
11	4FPH	229.4	225.95	3.4476	0.1478
12	4APH	248.1	247.48	0.6212	0.0266
13	4HOPH	237.3	234	3.2988	0.1414
14	4MPH	259.9	268.02	-8.116	-0.348
15	4EtPH	298.8	327.72	-28.92	-1.24
16	4HOPHA	326	342.77	-16.77	-0.719
17	4HOBN	268.2	228.91	39.285	1.6844
18	4PHOPH	413.4	392.59	20.806	0.8921
19	BiSPHA	519.7	453.83	65.866	2.8241
20	4BRPH	272.7	267.92	4.7816	0.205
21	4tBPH	370.3	392.66	-22.36	-0.959
22	3NPH	277.7	285.58	-7.884	-0.338
23	3HOPHA	326	351.37	-25.37	-1.088
24	3CLPH	258.1	271.27	-13.17	-0.565
25	3tBPH	370.3	352.85	17.447	0.7481

Continue……..

S. No.	Abbreviations	Parachor ± 4.0cm^3	*Predicted Parachor ± 4.0cm3*	*Residuals*	*Standard Residuals*
26	3MPH	259.9	253.62	6.2774	0.2691
27	3MOPH	278.9	268.61	10.292	0.4413
28	3DMAPH	324.3	290.44	33.863	1.4519
29	3EtPH	298.8	310.3	-11.5	-0.493
30	3BRPH	272.7	260.77	11.931	0.5116
31	3HOBN	268.2	218.85	49.346	2.1158
32	3FPH	229.4	240.15	-10.75	-0.461
33	3HOPH	237.3	247.79	-10.49	-0.45
34	3APH	248.1	257.59	-9.489	-0.407
35	2MPH	259.9	258.44	1.4566	0.0625
36	2CLPH	258.1	263.81	-5.707	-0.245
37	2FPH	229.4	248.02	-18.62	-0.798
38	2MOPH	278.9	325.43	-46.53	-1.995

39	2EtPH	298.8	350.92	-52.12	-2.235
40	2HOPH	237.3	253.29	-15.99	-0.686
41	4M2HOPH	274.9	279.98	-5.075	-0.218
42	2APH	248.1	262.06	-13.96	-0.598
43	2HOBN	268.2	218.74	49.461	2.1207
44	2NPH	277.7	289.36	-11.66	-0.5
45	2BRPH	272.7	290.02	-17.32	-0.742
46	2tBPH	370.3	349.45	20.853	0.8941
47	4PRPH	338.6	353.23	-14.63	-0.627
48	4BPH	378.4	364.82	13.582	0.5823
49	4PPH	418.2	388.13	30.071	1.2893

III. Result And Discussion

In case of modeling Parachor to build linear relationship and test model, the 49 compound data sets was used as training to build models. With the selected eight to ten different descriptors, we will build linear models using the training data sets and equations (1) and (2) were obtained. QSAR & QSPR attempts to find consistent relationship between physiochemical properties and molecular structure, so that these "Relationship Rules" can be used to evaluate the activity and properties of new compounds.

In order to confirm most powerful predictable Model for Parachor we have apply some statistical parameter[7]. These statistical parameters are support Model-II for Parachor due to low value of **LSE** and PE is much greater than **R** for model-II (Eq.2); is the better model compares to other. The cross-validated **PRESS and SSY** as recorded in **Table (1.1)** indicates model-II (Eq.2) for Parachor is a better model and will give excellent result. And according to **SPRESS** and **PSE** values model-II (Eq.2) is a better model and will also give excellent result.

Table (1.1) Statistical parameters for Model I, and Model II

S. No.	Statistical parameters	Model I	Model II
1	**N**	**49**	**49**
2	**no of Descriptors**	**8**	**8**
3	**R**	**0.860**	**0.934**
4	**R^2**	**0.740**	**0.873**
5	**SE or Sd**	**36.557**	**25.549**
6	**PRESS**	**53457.816**	**26110.859**
7	**SSY**	**151835.566**	**179182.523**
8	**R^2cv**	**1.840**	**5.862**
9	**SPRESS**	**36.557**	**25.549**
10	**PSE**	**33.030**	**23.084**
11	**R^2A**	**0.688**	**0.847**
12	**LSE**	**53457.816**	**26110.859**
13	**PE**	**0.596**	**0.584**
14	**Q=r/sd**	**0.024**	**0.037**
15	**PRESS/SSY**	**0.352**	**0.146**

IV. Conclusion

By the study of Parachor of phenols derivatives as anti-leukaemia agents, models discussed earlier Model II shows excellent result in prediction of TPSA. Statistical approach PRESS, SSY, SPRESS, PSE values supported this model. Higher Q and Lower LSE values give it to best prediction power.

Observed value of Parachor was plotted against and Predicted values Using Eq. (2) shown in Figure below. The figure clearly indicates there is a significant co-relation between Observed and Predicted values of Parachor. Only 2HOBN, 3FPH, 3DMAPH, 3HOPHA, 4HOBN, 4PHOPH, BiSPHA, 4HOBAL [2-hydroxybenzonitrile, 3-fluorophenol, 3-(dimethylamino)phenol, N-(3-hydroxyphenyl)acetamide, 4-hydroxybenzonitrile, 4-phenoxyphenol, Bisphenol-A (4,4'-propane-2,2-diyldiphenol), 4-hydroxybenzaldehyde respectively] shows deviation. Other molecule shows excellent co-relation for Parachor. (Correlation coefficient is 0.9342, r^2 is 0.8728).

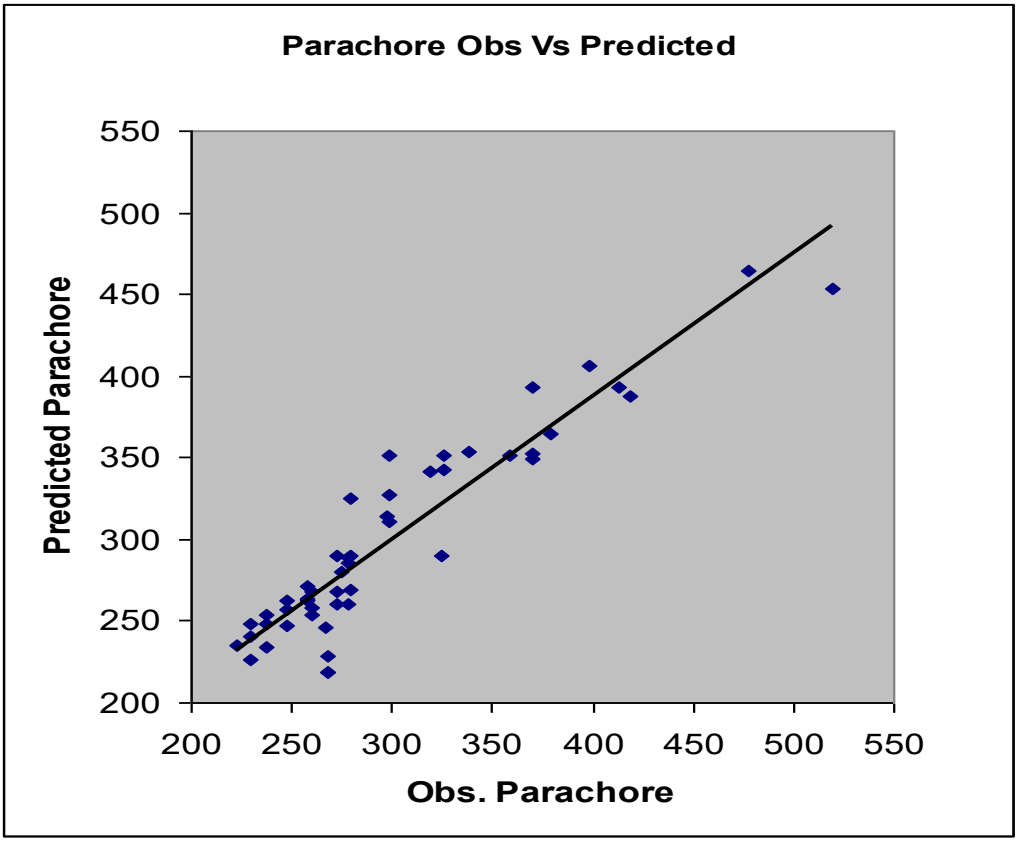

Figure 1.1 Correlation of Observed and Predicted value of Parachor Using Eq. (2)

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