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Modelling of Molar Refractivity of phenols derivatives as anti-leukaemia agents by computational method

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ABSTRACT: Molar refractivity is related, not only to the volume of the molecules but also to the London dispersive forces that act in the drug-receptor interaction. In this study different molecular models have been used to describes Molar Refractivity of phenols derivatives as anti-leukaemia agents. To developing the models for Molar Refractivity of phenol derivatives we used descriptors like Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e, eHOMO, eLUMORDF045m, MATS5p, R3e and the best model proposed for Molar Refractivity. for this we used several statistical parameters like R, PRESS, R^2cv, SSY, SPRESS, PSE, LSE, PE etc. to validate the model.

KEYWORDS: Molar refractivity, QSAR, Molecular descriptors, 3D MoRSE descriptors,FDI descriptors, RDF descriptors, Moreau autocorrelation descriptors, correlation coefficient.

I. INTRODUCTION

In the drug design process in 1997, Christopher Lipinski proposed a set of rules for drug likeness. However, additional features that increase drug likeness have been suggested, including molar refractivity from 40 to 130 (molar refractivity is a measure the overall polarity of a molecule). There are three major forces that are important in biochemical ligand binding: hydrophobic, dispersive, and electrostatic interactions. Molar refractivity is related to dispersive forces, and the molecular orbital charge distribution or the electrostatic potential at the van der Waals radius may be used for modelling the electrostatic interaction.

The theoretical basis for using Molar refractivity [1] as a free-energy related parameter in studying drug-receptor interaction and quantitative structure-activity relationship (QSAR) is presented in this paper. Molar refractivity is a measure of the total polarizability of a mole of a substance and is dependent on the temperature, the index of refraction, and the pressure. The molar refractivity is defined as

$$A = \frac{4\pi}{3} N_A \alpha,$$

where $N_A \approx 6.022 \times 10^{23}$ is the Avogadro constant and α is the mean polarizability of a molecule. Substituting the molar refractivity into the Lorentz-Lorenz formula gives

$$A = \frac{RT}{p} \frac{n^2 - 1}{n^2 + 2}$$

For a gas, $n^2 \approx 1$, so the molar refractivity can be approximated by

$$A = \frac{RT}{p} \frac{n^2 - 1}{3}.$$

In SI units, R has units of J mol^{-1} K^{-1}, T has units K, n has no units, and p has units of Pa, so the units of A are m^3 mol^{-1}.

In terms of density, ρ molecular weight, M it can be shown that:

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$$A = \frac{M}{\rho}\frac{n^2-1}{n^2+2} \approx \frac{M}{\rho}\frac{n^2-1}{3}.$$

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

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

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. For a radiation of infinite wavelength, the molar refractivity represents the real volume of the molecules. Molar refractivity is related, not only to the volume of the molecules but also to the London dispersive forces that act in the drug-receptor interaction[2].

According to S. Gladstone[3], the first attempts of making a rational partition of the molar refractivity in the involved electronic groups were A.L. von Steiger in 1921, K. Fajans in 1924 and C. P. Smith in 1925. Nevertheless, the importance of splitting the molar refractivity in their atomic component for QSAR studies guided to three-dimensional molecules has been demonstrated by Crippen et al. A method for the estimation of molar refractivity, based on the assignment of 22 atomic contributions obtained by classification of each atomic fragment according to the number and nature of the connected atoms to him, was developed by those authors[4-7].

II. MATERIAL AND METHOD

Modelling of Molar Refractivity of Phenol derivatives we used 3D MoRSE descriptors (3D Molecule Representation of Structures based on Electron diffraction),FoldingDegree 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 Molar Refractivity of phenol derivatives in we used eight descriptors Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e, eHOMO, eLUMO. There are 49 observations (molecules) are used to build first model for Molar Refractivity**.** By regression Statistics we get correlation coefficient is 0.8519, r^2 is 0.7257, Adjusted R Square *is* 0.6709, and Standard Error is4.7642 for model-I which described by equation 1.

Predicted **MR= (**4.173723 x Mor04m**) + (**-30.3463 x Mor23m**) + (**-137.064 x FDI**) + (**1.047213 x RDF045m**) + (**-0.04139 x MATS5p**)+ (**14.43368 x R3e**) + (**0.955974 x eHOMO**) + (**0.731685 x eLUMO**) +**154.5974

…..(1)

Analysis of variance of Model -I for Molar Refractivity

	df	*SS*	*MS*	*F*	*Significance F*
Regression	8	2402.2	300.27	13.229	4.15E-09
Residual	40	907.9	22.697		
Total	48	3310.1			

To developing the second model for Molar Refractivity 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 second model for Molar Refractivity**.** By regression Statistics we get correlation coefficient is 0.9308, r^2 is 0.8664, Adjusted R Square *is* 0.8396, and Standard Error is3.3256 for model-II which described by equation 2.

Predicted **MR= (**8.360886 x Mor29p**) + (**13.12016 x Mor20e**) + (**5.329599 x Mor04m**) + (**-8.83453 x Mor23m**) + (**-190.042 x FDI**) + (**1.092348 x RDF045m**) +(**-0.37511 x MATS5p**) + (**10.91803 x R3e**) +**199.2

…..(2)

Analysis of variance of Model -II for Molar Refractivity

	df	*SS*	*MS*	*F*	*Significance F*
Regression	8	2867.7	358.46	32.412	3.89E-15
Residual	40	442.38	11.06		
Total	48	3310.1			

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Table (i) Observed and Predicted value of Molar Refractivity Using Eq. (2)

S No.	Substituents	Molar Refractivity ± 0.3cm3	*Predicted Molar Refractivity ± 0.3cm3*	*Residuals*	*Standard Residuals*
1	4-OCH3	34.81	*37.177*	*-2.367*	*-0.78*
2	4-OC2H5	39.44	*43.778*	*-4.338*	*-1.429*
3	4-OC3H7	44.07	*42.39*	*1.6802*	*0.5534*
4	4-OC4H9	48.71	*50.676*	*-1.966*	*-0.648*
5	4-OC6H13	57.97	*57.422*	*0.5476*	*0.1804*
6	H	28.13	*29.801*	*-1.671*	*-0.55*
7	4-NO2	34.67	*32.573*	*2.0975*	*0.6909*
8	4-Cl	33.02	*33.902*	*-0.882*	*-0.29*
9	4-I	41.04	*42.737*	*-1.697*	*-0.559*
10	4-CHO	34.88	*31.255*	*3.6246*	*1.1939*
11	4-F	28.12	*28.041*	*0.0791*	*0.0261*
12	4-NH2	32.37	*30.659*	*1.7113*	*0.5637*
13	4-OH	30.01	*29.148*	*0.8625*	*0.2841*
14	4-CH3	32.95	*33.625*	*-0.675*	*-0.222*
15	4-C2H5	37.68	*40.846*	*-3.166*	*-1.043*
16	4-NHCOCH3	42.4	*43.842*	*-1.442*	*-0.475*
17	4-CN	32.84	*28.87*	*3.9697*	*1.3076*
18	4-OC6H5	54.57	*50.131*	*4.439*	*1.4622*
19	Bisphenol-A	68.16	*58.954*	*9.2058*	*3.0324*
20	4-Br	35.82	*35.062*	*0.7576*	*0.2496*
21	4-C (CH3)3	46.52	*49.482*	*-2.962*	*-0.976*
22	3-NO2	34.67	*35.539*	*-0.869*	*-0.286*
23	3-NHCOCH3	42.4	*44.972*	*-2.572*	*-0.847*
24	3-Cl	33.02	*34.724*	*-1.704*	*-0.561*

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25	3-C(CH3)3	46.52	*45.396*	*1.1245*	*0.3704*
26	3-CH3	32.95	*31.717*	*1.2327*	*0.406*
27	3-OCH3	34.81	*34.084*	*0.7259*	*0.2391*
28	3-N (CH3)2	42.44	*37.471*	*4.9694*	*1.6369*
29	3-C2H5	37.68	*38.734*	*-1.054*	*-0.347*
30	3-Br	35.82	*33.937*	*1.8831*	*0.6203*
31	3-CN	32.84	*27.335*	*5.5048*	*1.8133*
32	3-F	28.12	*30.232*	*-2.112*	*-0.696*
33	3-OH	30.01	*31.297*	*-1.287*	*-0.424*
34	3-NH2	32.37	*32.309*	*0.0614*	*0.0202*
35	2-CH3	32.95	*32.533*	*0.4171*	*0.1374*
36	2-Cl	33.02	*34.052*	*-1.032*	*-0.34*
37	2-F	28.12	*31.389*	*-3.269*	*-1.077*
38	2-OCH3	34.81	*41.804*	*-6.994*	*-2.304*
39	2-C2H5	37.68	*44.042*	*-6.362*	*-2.096*
40	2-OH	30.01	*32.161*	*-2.151*	*-0.708*
41	2-OH, 4CH3	34.84	*35.239*	*-0.399*	*-0.132*
42	2-NH2	32.37	*33.103*	*-0.733*	*-0.241*
43	2-CN	32.84	*27.66*	*5.1802*	*1.7064*
44	2-NO2	34.67	*36.509*	*-1.839*	*-0.606*
45	2-Br	35.82	*37.658*	*-1.838*	*-0.605*
46	2-C (CH3)3	46.52	*45.005*	*1.5151*	*0.4991*
47	4-C3H7	42.31	*43.929*	*-1.619*	*-0.533*
48	4-C4H9	46.94	*45.249*	*1.6915*	*0.5572*
49	4-C5H11	51.58	*47.863*	*3.7172*	*1.2245*

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III. RESULT AND DISCUSSION

Molar refractivity is a measure of the total polarizability of a mole of a substance and is dependent on the temperature, the index of refraction, and the pressure. In case of modeling Molar Refractivity to build linear relationship and test model, the 49 compound data sets were used as training to build model. Finally with the selected eight 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 Molar Refractivity we have apply some statistical parameter[8]. These statistical parameters are support Model II for Molar Refractivity and result of those are the follows. The cross-validated **PRESS and SSY** as recorded in '**Table (i)**indicates model-II (Eq.2) for Molar Refractivity is a better model and will give excellent result. And according to **SPRESS** and **PSE** valuesmodel-II is a better model and will also give excellent result. The **PE** values are much greater thancorrelation coefficients R for Molar Refractivity model-II.So, it has best predictive powers. The **LSE** values are low for Molar Refractivity model-II has support this model.

Table (ii) 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	0.852	0.931
4	R^2	0.726	0.866
5	SE or Sd	4.764	3.326
6	PRESS	907.899	442.380
7	SSY	2402.152	2867.672
8	R^2cv	1.646	5.482
9	SPRESS	4.764	3.326
10	PSE	4.304	3.005
11	R^2A	0.671	0.840
12	LSE	907.899	442.380
13	PE	0.598	0.584
14	Q=r/sd	0.179	0.280
15	PRESS/SSY	0.378	0.154

IV. CONCLUSION

By the study of Molar Refractivity of phenols derivatives as anti-leukaemia agents, models discussed earlier Model II shows excellent result in prediction of Molar Refractivity. 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 Molar refractivitywas 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 Molar refractivity. Only 4IPH(4-iodophenol), 3DMAPH(3-(dimethylamino)phenol), 3HOBN(3-hydroxybenzonitrile), 2MOPH(2-methoxyphenol), 2EtPH(2-ethylphenol), 2HOBN(2-hydroxybenzonitrile)shows deviation. Other molecule shows excellent co-relation for Molar refractivity. (Correlation coefficient is 0.9308, r^2 is 0.8664).

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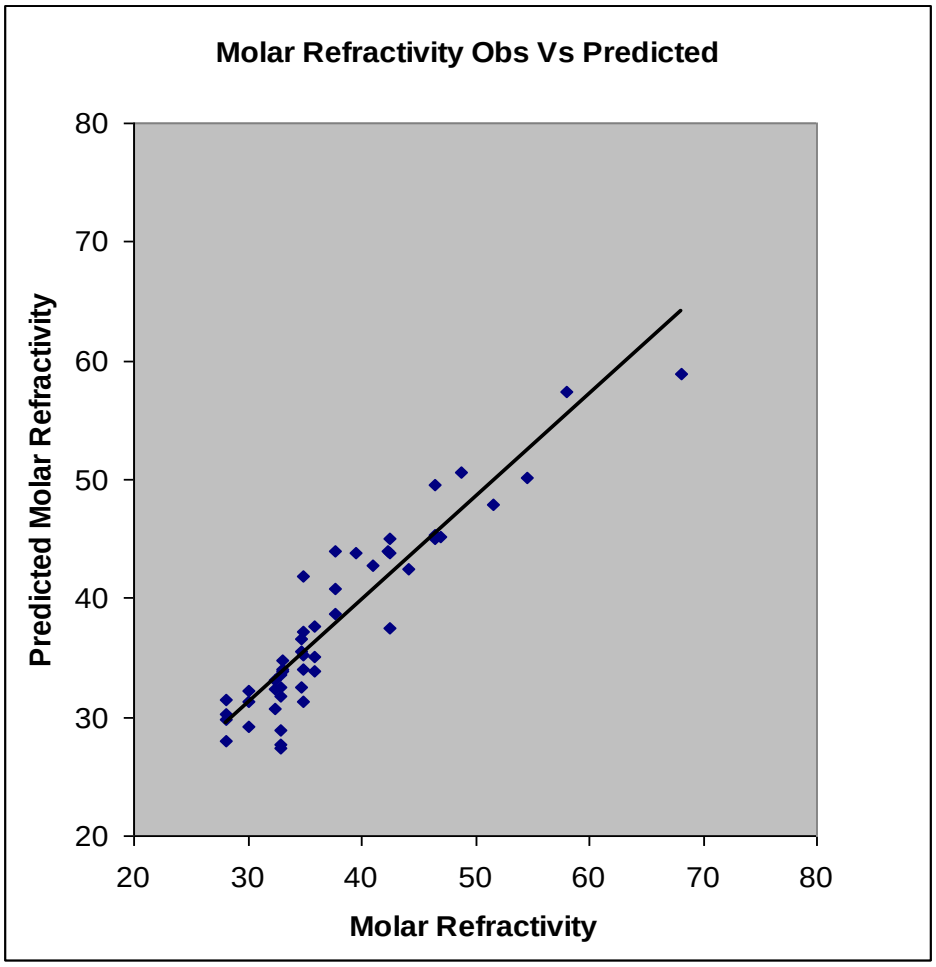

Figure1.1 Correlation of Observed and Predicted value of Molar refractivity Using Eq. (2)

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