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QSPR STUDY BY MICROSOFT EXCEL FOR CEPHALOSPORIN

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ABSTRACT

Molar refractivity is important property of many drugs to be measured. Refractive index measurement of drugs and their solutions is valuable for their uses in optical organs. However, refractive index and hence molecular refractivity is also helpful in prediction of suitability of drugs through oral dose with the help of Lipinski's rule of five and it's modification. Molecular refractivity can be measured practically as well as calculated with the help of software. In present research work molecular refractivity of selected series of cephalosporin compounds were calculated with the help of chemsketch software. Similarly, molecular descriptors of the same selected compounds were also calculated with the help of suitable Dragon software. Then regression model was developed by using former and later data. As the application of regression equation one compound of cephalosporin viz. Cefbuperazone was modified to minimize molecular refractivity. During modification toxicity was also controlled / minimized by considering regression model for median lethal dose for the same series of compounds. Development of M L Regression was carried out with the help of Micro Soft Excel software through Forward selection method. In which, selection of independent variable was done on the basis of lowest p-value. P-value shows the significance of considered independent variable for the prediction of dependent variable involved in MLR equation/ model. Less p-value shows more predictability. If p-value is greater than 0.05 for any one independent variable i.e. predictability is less than 50% then such type of regression is not significant.

Key words: *MS Excel, Molar refractivity, p-value, MLR, Forward selection method, Correlation.*

I. INTRODUCTION

Molar refractivity ($ń_{mol}$) is related to refractive index (η_r). Refractive index [1] of a substance can be defined as the ratio of velocity of light in vacume to that in the medium. The refractive index can be measured with high degree of accuracy. For practical determination of η_r Abbe refractometer is applied. This can also be estimated with the help of many available softwares.

$\eta_r = \text{Sin i/ Sin r} \quad \rightarrow (1)$

Where, i = angle of incidence, r = angle of refraction.

The molar refractivity reflects arrangements of the electron shells of ions in molecules and yields information about the electronic polarization of ions. The combination of ions to form molecules in a gas or a crystal or complex ions in solution is always accompanied by a change in the properties of the ions themselves. The molar refractivity reflects the changes in the properties due to polarization or to deformation of the electron shells of the ions under the influence of the electric fields of neighbouring ions. Molecular refractivity is constitutive-additive property dependent upon refractivity (η) and molar volume (V_m) as shown by following Lorenz-Lorentz equation.

$$\text{Molar Refractivity} = ń_{mol} = \frac{(\eta^2-1)M}{(\eta^2+1)d} \quad \rightarrow (2)$$

$$\text{Molar Refractivity} = \frac{(\eta^2-1)}{(\eta^2+1)} * \text{Molar volume} \quad \rightarrow (3)$$

where, η = refractive index, $\text{Molar volume} = \frac{M}{d} \rightarrow (4)$

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

However, molar refractivity of various compounds can be estimated by various software by using their chemical 2D and 3D structure saved in mol files or other file formate according to suitability of calculating software. Presently many software viz. chem sketch, chem draw, dragon etc. which can calculate molar refractivity by only their 2D or 3D structure.

II. RESEARCH METHODOLOGY

Computer softwares used in present research work

All calculations were run on a Acer personal computer (laptop, model Acer ASPIRE 4530) with a Pentium IV configuration and windows XP as operating system and AMD Athlon-X_2 processer. All of above mentioned topological indices can be calculated by using suitable computer operated software. For this purpose DRAGON verson 5.5- 2007 [2, 3], applied. This software can accept various molecular structure in the form of separate files developed by Hyperchem or ACD LAB's Chemsketch version 12.0 or some specified softwares. DRAGON software [4] can calculate 3224 descripters including all of above. The molecular structures of data set were sketched using Chemsketch version 12.0, for developing DRAGON acceptable molecular structure file Chemsketch is to be applied which export chemical file as MDL files. Chemsketch is a ACD LAB product [5]. ACD Lab's Chem Sketch 12.0 suitable for Microsoft Window. ACD/Chem Sketch is the powerful all-purpose chemical drawing and graphics launched by ACD Labs which help chemists quickly and easily draw molecular structures, reactions, and schematic diagrams. This can calculate chemical properties also. This can draw Chemical structure and graphical images. Chemsketch can save molecules in various types of file format e.g. MDL, mol and PDF format etc. For statistical analysis like correlation, regression and validation etc. Microsoft Office Excel, software [6] applied during research work. Microsoft Office Excel 2007 is the part of Microsoft office professional edition 2007 developed by Microsoft Corporation.

QSPR STUDY FOR MOLAR REFRACTIVITY ($ή_{mol}$)

Data generation:

For molar refractivity 50 molecules set ($C^1 – C^{50}$) were selected [as given in Table (1)]. Molecular refractivity data calculated by chem sketch [given in Table (1)] for the selected set of molecules. The indices were calculated by Dragonsoftware. The variation of molar refractivity with calculated indices and distribution of various indices given in Chart (1)

Table (1): Values of $ή_{mol}$ and mostpredictive indices

Set	Name	Molecularformula ofmolecules	Molar Refractivity [$ή_{mol}$]$_{(\pm 0.4 cm^3)}$	X^1	T(N-S)	T(N-O)	$(Mor_{01u})^w_{ox}$	$(S_s)^{wox}$	W	J
C^1	Cefacetrile	$C_{14}H_{17}N_3O_6S$	76.8	*10.4*	*10*	*91*	496	56.2	*1073*	*2.02*
C^2	Cefadroxil	$C_{16}H_{17}N_3O_5S$	90.94	*11.8*	*9*	*76*	741	68.8	*1570*	*1.57*
C^3	Cefalexin	$C_{15}H_{15}N_3O_4S$	85.0	*11.1*	*9*	*53*	703	63.2	*1242*	*1.56*
C^4	Cefaloglycin	$C_{18}H_{19}N_3O_6S$	100.5	*13.3*	*9*	*101*	703	63.2	*2172*	*1.58*
C^5	Cefroxadine	$C_{16}H_{17}N_3O_5S$	91.78	*11.9*	*9*	*71*	703	62.2	*1548*	*1.59*
C^6	Cefaclore	$C_{15}H_{14}ClN_3O_4S$	89.61	*11.4*	*9*	*53*	703	63.2	*1383*	*1.58*
C^7	Cefradine	$C_{16}H_{17}N_3O_4S$	89.0	*11.4*	*9*	*44*	780	62.2	*1383*	*1.58*
C^8	Cefonicid	$C_{17}H_{16}N_6O_8$	121.31	*16.1*	*69*	*315*	666	65.2	*3766*	*1.33*
C^9	Cefprozil	$C_{18}H_{19}N_3O_5S$	100.11	*12.8*	*9*	*76*	741	68.8	*1954*	*1.58*
C^{10}	Cefatrizine	$C_{18}H_{18}N_6O_5S_2$	113.19	*14.9*	*56*	*233*	741	68.8	*2945*	*1.31*
C^{11}	Cefalothin	$C_{16}H_{16}N_2O_6S_2$	95.07	*12.4*	*14*	*52*	528	57.2	*1790*	*1.56*
C^{12}	Cefalonium	$C_{20}H_{19}N_4O_5S_2$	116.91	*14.8*	*54*	*152*	528	57.2	*2975*	*1.31*

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C^{13}	Cefaloridine	$C_{19}H_{17}N_3O_4S_2$	108.77	*13.5*	*29*	*51*	496	58.2	*2180*	*1.33*
C^{14}	Cefoxitin	$C_{16}H_{17}N_3O_6S_2$	98.73	*12.8*	*31*	*79*	666	62.6	*1837*	*1.70*
C^{15}	Cefazoline	$C_{14}H_{14}N_8O_4S_3$	109.76	*13.9*	*172*	*224*	465	60.7	*2468*	*1.30*
C^{16}	Ceftezole	$C_{14}H_{16}N_8O_3S_3$	108.91	*13.5*	*172*	*175*	465	60.7	*2223*	*1.31*
C^{17}	Cefapirine	$C_{16}H_{15}N_3O_6S_2$	98.11	*12.9*	*21*	*119*	528	60.7	*2008*	*1.54*
C^{18}	Cefazedone	$C_{18}H_{15}Cl_2N_5O_5S_3$	126.33	*15.6*	*73*	*177*	630	73.9	*3579*	*1.29*
C^{19}	Cefazaflur	$C_{13}H_{13}F_3N_6O_4S_3$	101.73	*13.6*	*105*	*166*	435	74.8	*2470*	*1.54*
C^{20}	Cefuroxime	$C_{16}H_{16}N_4O_8S$	96.66	*13.8*	*15*	*185*	666	67.5	*2349*	*1.62*
C^{21}	Cefuzonam	$C_{16}H1_5N_7O_5S_4$	123.08	*15.4*	*192*	*246*	703	70.5	*3133*	*1.35*
C^{22}	Cefmetazole	$C_{15}H_{17}N_7O_5S_3$	114.46	*14.4*	*130*	*254*	595	64.9	*2591*	*1.64*
C^{23}	Cefotatam	$C_{17}H_{17}N_7O_8S_4$	131.49	*17.0*	*196*	*516*	820	87.2	*4350*	*1.37*
C^{24}	Cefbuperazon	$C_{21}H_{27}N_3$	143.49	*19.3*	*108*	*682*	1225	98.4	*6176*	*1.38*
C^{25}	Cefminoxime	$C_{16}H_{21}N_7O_7S_3$	120.77	*15.6*	*130*	*426*	741	79.4	*3492*	*1.59*
C^{26}	Cefacapene	$C_{17}H_{19}N_5O_6S_2$	109.5	*14.2*	*52*	*207*	820	67.5	*2584*	*1.62*
C^{27}	Cefdaloxime	$C_{14}H_{15}N_5O_6S_2$	95.53	*12.9*	*42*	*189*	595	71.0	*1903*	*1.62*
C^{28}	Cefdinir	$C_{14}H_{13}N_5O_5S_2$	94.14	*12.4*	*42*	*144*	595	71.0	*1701*	*1.62*
C^{29}	Cefmatilen	$C_{15}H_{14}N_8O_5S_4$	121.17	*15.4*	*222*	*307*	595	71.0	*3225*	*1.31*
C^{30}	Ceftobiprole	$C_{21}C_{24}N_8O_6S$	124.6	*17.3*	*48*	*365*	630	71.8	*4333*	*1.19*
C^{31}	Cefditoren	$C_{25}H_{28}N_6O_7S_3$	156.27	*19.4*	*119*	*327*	820	70.0	*6137*	*1.41*
C^{32}	Cefatamet	$C_{14}H_{15}N_5O_6S_2$	94.49	*12.3*	*42*	*144*	703	70.6	*1693*	*1.63*
C^{33}	Cefminoxim	$C_{15}H_{15}N_5O_7S_2$	122.09	*15.8*	*177*	*338*	703	70.6	*3413*	*1.35*
C^{34}	Cefpodizime	$C_{20}H_{22}N_6O_7S_4$	135.56	*17.2*	*162*	*350*	703	70.6	*4530*	*1.31*
C^{35}	Cefotaxime	$C_{17}H_{19}N_5O_6S_2$	105.95	*14.2*	*42*	*244*	703	70.6	*2584*	*1.62*
C^{36}	Cefpodoxime	$C_{16}H_{21}N_5O_6S_2$	100.49	*13.4*	*42*	*189*	703	70.6	*2096*	*1.63*
C^{37}	Cefteram	$C_{19}H_{18}N_6O_7S_4$	114.28	*15.3*	*114*	*308*	703	70.6	*3081*	*1.37*
C^{38}	Cefepime	$C_{20}H_{28}N_6O_5S_2$	114.52	*15.2*	*58*	*180*	666	71.5	*3029*	*1.40*
C^{39}	Cefozopran	$C_{19}H_{19}N_9O_5S_2$	126.65	*16.9*	*107*	*312*	666	71.5	*3932*	*1.21*
C^{40}	Ceftiofur	$C_{19}H_{17}N_5O_7S_3$	125.23	*16.3*	*87*	*259*	703	70.5	*3753*	*1.34*
C^{41}	Ceftiolene	$C_{20}H_{18}N_8O_8S_3$	140.22	*18.7*	*163*	*549*	703	70.5	*5623*	*1.32*
C^{42}	Ceftizoxime	$C_{13}H_{13}N_5O_5S_2$	90.07	*11.9*	*42*	*144*	703	70.6	*1531*	*1.61*
C^{43}	Ceftriaxone	$C_{18}H_{18}N_8O_7S_3$	129.96	*17.1*	*152*	*435*	703	70.6	*4386*	*1.35*
C_{44}	Cefpirome	$C_{22}H_{22}N_6O_5S_2$	130.41	*16.9*	*58*	*180*	703	70.6	*3906*	*1.22*
C_{45}	Cefexime	$C_{16}H_{17}N_9O_5S_3$	105.60	*14.2*	*42*	*218*	820	84.7	*2560*	*1.63*
C_{46}	Cefpimizole	$C_{28}H_{26}N_6O_{10}S_2$	161.10	*21.8*	*116*	*554*	1275	95.8	*8803*	*1.17*
C_{47}	Ceftibuten	$C_{15}H_{14}N_4O_6S_2$	96.19	*12.8*	*32*	*154*	820	80.2	*1897*	*1.62*
C_{48}	Cefoperazone	$C_{25}H_{27}N_9O_8S_2$	158.18	*21.0*	*108*	*646*	1225	86.5	*7383*	*1.23*
C_{49}	Ceftazidime	$C_{22}H_{22}N_6O_7S_2$	135.01	*17.5*	*58*	*282*	1035	89.4	*4573*	*1.40*
C_{50}	Cefovecin		107.35	*14.4*	*42*	*189*	703	70.5	*2506*	*1.40*

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Table (2):Values of less predictive indices for $\acute{\eta}_{mol}$

Set	*W'*	*H*	*T(N-N)*	T(N-O)	SMTI	$(Ss)^{wox}$	$(Mor_{01u})^{wox}$	$(Mor_{01am})^{wox}$	$(Mor_{01v})^{wox}$	$Mor_{01en})^{wox}$	$(Mor_{01p})^{wox}$	$(Ss)^{wor}$	$(Mor_{01u})^{wor}$	$(Mor_{01am})^{wor}$	$(Mor_{01v})^{wor}$	(Mor_{01en})wor	$(Mor_{01p})^{wor}$
C^{1}	*1815*	*39.4*	*14*	*91*	*4970*	56.2	496	296.8	194.8	548.5	215.8	61.8	496	296.8	194.8	548.5	215.8
C^{2}	*2690*	*46.8*	*12*	*76*	*6763*	68.8	741	405.6	307.8	791.7	304.2	48.2	325	190.5	129.8	353.5	146.1
C^{3}	*2222*	*42.4*	*12*	*53*	*5319*	63.2	703	368.6	295.1	739.9	328.4	46.5	253	168.1	105.3	280.8	117.5
C^{4}	*3552*	*52.4*	*12*	*101*	*9062*	63.2	703	368.6	295.1	739.9	328.4	61.9	496	296.9	194.8	548.5	215.8
C^{5}	*2688*	*46.7*	*12*	*71*	*6543*	62.2	703	368.6	295.1	739.9	328.4	51.7	351	317.3	138.3	389.5	154.1
C^{6}	*2443*	*44.7*	*12*	*53*	*5882*	63.2	703	368.6	295.1	739.9	328.4	50.3	253	222.4	115.5	288.3	130.7
C^{7}	*2443*	*44.7*	*12*	*44*	*5882*	62.2	780	368.6	295.1	739.9	328.4	48.2	325	190.5	129.8	353.5	146.1
C^{8}	*6178*	*66.1*	*67*	*315*	*16036*	65.2	666	370.7	283.4	710.3	314.4	83.2	630	592.7	278.6	735.2	318.1
C^{9}	*3228*	*50.6*	*12*	*76*	*8175*	68.8	741	405.6	307.8	791.7	340.2	52.2	435	235.6	174.9	464.5	197.2
C^{10}	*4785*	*59.4*	*99*	*233*	*12709*	68.8	741	405.6	307.8	791.7	340.2	61.7	528	384.4	232.8	580.9	263.9
C^{11}	*2946*	*48.1*	*3*	*52*	*7526*	57.2	528	346.2	237.2	562.9	275.5	61.8	496	296.8	194.8	548.6	215.8
C^{12}	*4827*	*59.3*	*40*	*152*	*12793*	57.2	528	346.2	237.2	562.9	275.5	72.0	780	439.52	325.3	836.5	356.8
C^{13}	*3780*	*53.3*	*14*	*51*	*9530*	58.2	496	343.9	230.5	531.8	266.5	60.5	595	337.36	252.5	633.1	284.7
C^{14}	*3045*	*51.4*	*16*	*79*	*7670*	62.6	666	415.5	285.5	713.1	330.2	65.8	561	328.22	215.0	620.4	237.4
C^{15}	*4075*	*55.1*	*191*	*224*	*10736*	60.7	465	317.6	197.9	519.2	212.3	62.7	595	459.95	270.5	646.1	324.4
C^{16}	*3727*	*52.9*	*191*	*175*	*9732*	60.7	465	317.6	197.9	519.2	212.3	61.0	496	422.91	234.6	546.5	278.6
C^{17}	*3320*	*49.9*	*18*	*119*	*8419*	60.7	528	375.4	245.9	570.2	281.2	61.8	496	296.85	194.8	548.6	215.8
C^{18}	*5724*	*63.5*	*69*	*177*	*15299*	73.9	630	540.7	302.5	704.7	338.3	62.7	595	459.95	270.5	646.1	321.4
C^{19}	*3911*	*54.1*	*67*	*166*	*12262*	74.8	435	385.4	182.9	513.9	205.8	64.2	595	420.08	254.8	654.8	287.8
C^{20}	*3697*	*54.4*	*39*	*185*	*9734*	67.5	666	409.9	281.4	730.7	306.9	63.8	465	298.74	183.2	522.8	200.5
C^{21}	*4927*	*61.5*	*166*	*246*	*13436*	70.5	703	488.2	304.8	772.1	343.2	61.0	496	422.9	234.6	546.5	278.1
C^{22}	*4105*	*56.6*	*144*	*254*	*10706*	64.9	595	389.2	248.7	647.2	286.7	69.6	741	496.07	304.8	816.0	343.6
C^{23}	*6438*	*70.5*	*150*	*516*	*18294*	87.2	820	667.3	362.3	925.6	418.8	69.6	741	496.07	304.8	816.0	343.6
C^{24}	*9151*	*81.6*	*294*	*682*	*25903*	98.4	1225	702.4	463.9	1361.2	502.4	70.1	630	459.6	266.6	703.5	298.9
C^{25}	*5225*	*62.5*	*144*	*426*	*14362*	79.4	741	501.1	303.3	822.9	344.4	69.6	741	496.1	304.8	816.0	343.6
C^{26}	*4020*	*56.6*	*72*	*207*	*10666*	67.5	820	480.9	347.8	867.2	399.4	69.8	465	298.4	183.2	522.8	200.5
C^{27}	*3116*	*50.8*	*46*	*189*	*7938*	71.0	595	452.1	266.5	662.8	298.5	53.2	435	242.6	166.2	474.3	186.7
C^{28}	*2835*	*48.9*	*46*	*144*	*7128*	71.0	595	452.1	266.5	662.8	298.5	51.2	351	210.6	146.3	380.6	163.7
C^{29}	*5069*	*61.2*	*236*	*307*	*13866*	71.0	595	452.1	266.5	662.8	298.5	63.5	561	460.3	256.7	618.2	302.6
C^{30}	*7008*	*71.8*	*222*	*365*	*18914*	71.8	630	412.2	264.6	700.7	283.8	71.8	1081	514.6	420.7	1136.1	468.9
C^{31}	*9357*	*79.8*	*106*	*327*	*25598*	70.0	820	525.6	345.6	889.8	391.1	61.8	741	442.7	322.0	781.9	371.3
C^{32}	*2805*	*48.8*	*46*	*144*	*7098*	70.6	703	488.2	304.8	772.1	343.2	48.2	325	190.5	129.8	353.5	146.1
C^{33}	*5431*	*63.8*	*276*	*338*	*14566*	70.6	703	488.2	304.8	772.1	343.2	64.2	595	420.1	254.8	654.8	287.8
C^{34}	*6928*	*69.3*	*101*	*350*	*19112*	70.6	703	488.2	304.8	772.1	343.2	75.8	741	573.3	335.1	815.3	392.7
C^{35}	*4020*	*56.6*	*46*	*244*	*10666*	70.6	703	488.2	304.8	772.1	343.2	61.8	496	296.8	495.8	548.5	215.8
C^{36}	*3370*	*52.7*	*46*	*189*	*8706*	70.6	703	488.2	304.8	772.1	343.2	53.2	435	242.6	166.2	474.3	186.7
C^{37}	*4941*	*62.1*	*246*	*308*	*13166*	70.6	703	488.2	304.8	772.1	343.2	62.3	561	347.9	231.0	616.4	250.2
C^{38}	*4863*	*62.5*	*91*	*180*	*12948*	71.5	666	485.5	297.4	735.5	333.2	58.2	820	350.9	300.4	850.4	342.4
C^{39}	*6956*	*69.8*	*264*	*312*	*17210*	71.5	666	485.5	297.4	735.5	333.2	66.3	780	434.7	329.9	831.8	361.3
C^{40}	*5765*	*65.6*	*46*	*259*	*16000*	70.5	703	488.2	304.8	772.1	343.2	69.3	630	449.6	283.4	691.9	322.3
C^{41}	*8634*	*75.8*	*234*	*549*	*23609*	70.5	703	488.2	304.8	772.1	343.2	89.0	861	645.2	343.9	965.6	423.8
C^{42}	*2562*	*46.5*	*46*	*144*	*6456*	70.6	703	488.1	304.8	772.1	343.2	46.5	253	168.1	105.3	280.8	117.5

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C^{43}	*6872*	*70.2*	*219*	*435*	*18532*	70.6	703	488.2	304.8	772.1	343.2	78.0	741	530.7	317.6	825.0	355.4
C_{44}	*6930*	*69.9*	*91*	*180*	*17100*	70.6	703	488.2	304.8	772.1	343.2	64.5	861	430.1	361.6	897.0	402.9
C_{45}	*3930*	*56.5*	*46*	*218*	*10576*	84.7	820	609.6	356.8	922.1	395.9	51.2	351	210.6	146.3	380.6	163.7
C_{46}	*12869*	*91.9*	*99*	*554*	*37294*	95.8	1275	747.3	538.5	1333.7	578.3	84.2	990	610.1	406.7	1076.5	461.8
C_{47}	*3038*	*50.4*	*29*	*154*	*7932*	80.2	820	561.3	359.2	899.2	403.6	46.5	253	168.1	105.3	280.8	117.5
C_{48}	*11123*	*88.4*	*294*	*646*	*31520*	86.5	1225	666.1	509.1	1311.2	555.1	64.2	595	420.1	254.8	654.8	287.8
C_{49}	*6924*	*72.5*	*91*	*282*	*19281*	89.4	1035	691.3	438.4	1141.2	488.6	60.67	595	337.4	257.5	633.0	284.7
C_{50}	*4162*	*58.4*	*46*	*189*	*10786*	70.5	703	488.2	304.8	772.1	343.2	55.5	561	293.1	216.1	601.6	243.8

Abbreviations used in Table (1) &(2) are as follows:
W= Weiner index; W' = Detour index; χ1 = Randic index; J = Balban index; H = Harary index; SMTI = Schultz molecular topological index; T(N-N) = Topological distances between N and N; T(N-S) = Topological distances between N and S; T(N-O) = Topological distances between N and O. $(Mor_{1u})^{wox}$, and $(Mor_{1am})^{wox}$, $(Mor_{1v})^{wox}$, $(Mor_{1en})^{wox}$, $(Mor_{1p})^{wox}$ = 3D MoRSE descriptors for selected set of molecules with out -X group unweighted and weighted by atomic mass, vander waal volume, electronegativity, polarizability respectively.

$(Mor_{1u})^{wor}$, and $(Mor_{1am})^{wor}$, $(Mor_{1v})^{wor}$, $(Mor_{1en})^{wor}$ $(Mor_{1p})^{wor}$ = 3D MoRSE descriptors for selected set of molecules with out -R group unweighted and weighted by
atomic mass, vander waal volume, electronegativity, polarizability respectively.

$(S_s)^{wox}$, $(S_s)^{wor}$ = Sum of Keir-Hall electro topological state for selected set of molecules with out -X group and –R group respectively.
(Superscript 'wox' and 'wor' shows values for structures with out –X group and with -R group respectively.)

Data processing and outcome with statistical validation:
The correlation study of molar refractivity with other selected indices [given in Table (3)] show that randic index has the strongest correlation (0.983) with molar refractivity, while other indices like weiner, harary, detour, SMTI also shows better correlation (~0.95) and 3D Morse viz. $(Mor_{1p})^{wor}$ $(Mor_{1en})^{wor}$ (~0.75 - 0.80) with molar refractivity. But when the molar refractivity proposed on the basis of randic index by single step linear regression analysis then in validation the correlation between predicted and observed molar refractivity was 0.967, so for increasing the correlation between predicted and observed molar refractivity and to make contribution of other satisfactory correlated and less correlated indices for prediction of molar refractivity a stepwise multilinear regression analysis carried out by means of forward selection. In stepwise linear regression variable indices are selected on the basis of lowest p-value. The details of correlation of molar refractivity ($\acute{\eta}_{mol}$) with selected indices and properties are given as follows [Table (3)]:

Table (3): Correlation of molar refractivity with selectedIndices

Indices	**Correlation**	**Indices**	**Correlation**
W	0.959	T(N-O)	0.839
χ1	0.983	SMTI	0.958
J	-0.760	$(S_s)^{wox}$	0.600
W'	0.965	$(Mor_{1u})^{wox}$	0.576
H	0.979	$(Mor_{1am})^{wox}$	0.663
T(N-N)	0.655	$Mor_{1v})^{wox}$	0.604
T(N-S)	0.630	$(Mor_{1en})^{wox}$	0.595
$(Mor_{1p})^{wox}$	0.610	$(Mor_{1am})^{wor}$	0.779
$(S_s)^{wor}$	0.611	$(Mor_{1v})^{wor}$	0.699
$(Mor_{1u})^{wor}$	0.742	$(Mor_{1en})^{wor}$	0.749
$(Mor_{1p})^{wor}$	0.804		

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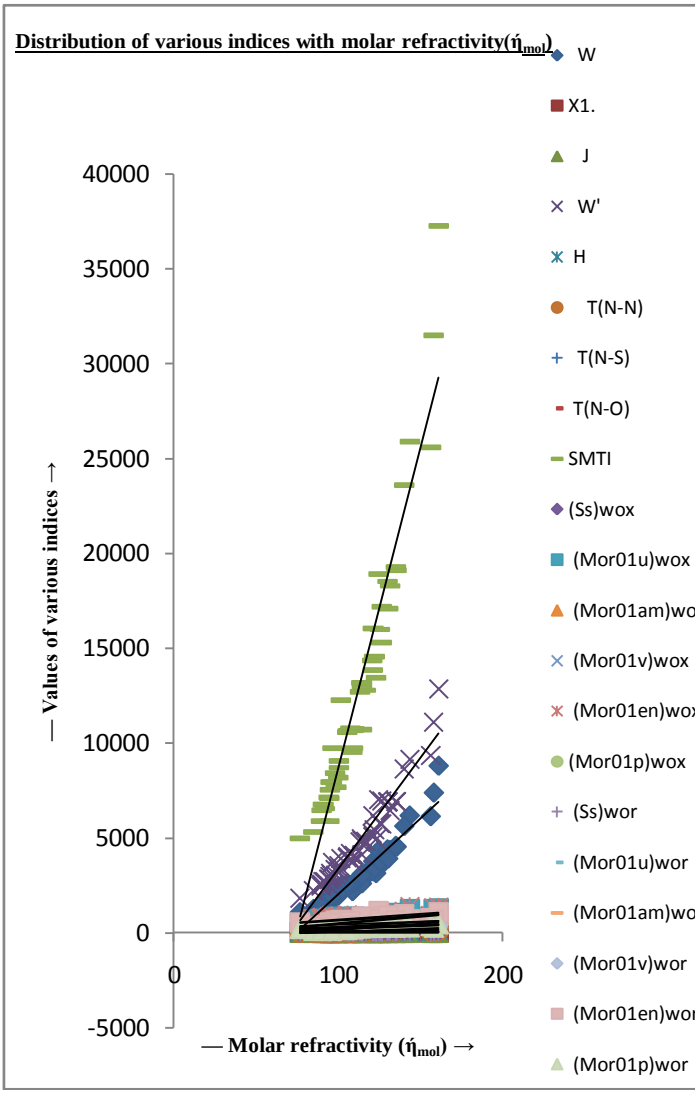

Chart (1) : Variation of ή$_{mol}$ with selected indices

Stepwise multilinearregression analysis for molar refractivity (ή$_{mol}$) can be described as follows:
Step-1: Searching for selection of first variable index.

Table (4) : Regression equations of individual indices for ή$_{mol}$

S. No.	Regression equations	Index	P-value of each independent variable
1	ή$_{mol}$ = 0.01(±0.0005) W + 77.53	W	4.34X10^{-28}
2	ή$_{mol}$ = 7.44(0.20) χ1 + 3.11	χ1	3.06 X10^{-37}
3	ή$_{mol}$ = - 86.01(±10.604) J + 238.82	J	1.5 X10^{-10}

ISSN 2348 – 8034
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4	$\acute{\eta}_{mol}$ =0.007(±0.0003) W' + 74.09	W'	1.28 X10^{-29}
5	$\acute{\eta}_{mol}$ = 1.62(±0.048) H + 16.91	H	9.08 X10^{-35}
6	$\acute{\eta}_{mol}$ = 0.14 (±0.02) T(N-N) + 98.97	T(N-N)	2.43 X10^{-7}
7	$\acute{\eta}_{mol}$ = 0.20(±0.04) T(N-S) + 96.74	T(N-S)	9.16 X10^{-7}
8	$\acute{\eta}_{mol}$ = 0.10 (±0.01) T(N-O) + 88.35	T(N-O)	2.7 X10^{-14}
9	$\acute{\eta}_{mol}$ = 0.002(±0.0001) SMTI + 539.13	SMTI	9.48X10^{-28}
10	$\acute{\eta}_{mol}$ = 1.26(±0.24) $(S_s)^{wox}$ + 24.16	$(S_s)^{wox}$	4.02 X10^{-6}
11	$\acute{\eta}_{mol}$ = 0.06(±0.01) $(Mor_{1u})^{wor}$ + 67.57	$(Mor_{1u})^{wor}$	1.2 X10^{-5}
12	$\acute{\eta}_{mol}$ = 0.12(±0.02) $(Mor_{1am})^{wox}$ + 55.58	$(Mor_{1am})^{wox}$	1.54 X10^{-7}
13	$\acute{\eta}_{mol}$ = 0.17(±0.03) $(Mor_{1v})^{wox}$ + 61.26	$(Mor_{1v})^{wox}$	3.4 X10^{-6}
14	$\acute{\eta}_{mol}$ = 0.06(±0.01) $(Mor_{1en})^{wox}$ + 64.98	$(Mor_{1en})^{wox}$	5.17 X10^{-6}
15	$\acute{\eta}_{mol}$ = 0.16(±0.03) $(Mor_{1p})^{\mathbf{wox}}$ + 58.90	$(Mor_{1p})^{\mathbf{wox}}$	2.48 X10^{-6}
16	$\acute{\eta}_{mol}$ = 1.33(±0.21) $(S_s)^{wor}$ + 30.09	$(S_s)^{wor}$	5.2 X10^{-8}
17	$\acute{\eta}_{mol}$ = 0.083(±0.013) $(Mor_{1u})^{wor}$ + 70.59	$(Mor_{1u})^{wor}$	6.88 X10^{-10}
18	$\acute{\eta}_{mol}$ = 0.12(±69.20) $(Mor_{1am})^{wor}$ + 69.20	$(Mor_{1am})^{wor}$	2.64 X10^{-11}
19	$\acute{\eta}_{mol}$ = 0.15(±0.02) $(Mor_{1v})^{wor}$ + 75.89	$(Mor_{1v})^{wor}$	1.69 X10^{-8}
20	$\acute{\eta}_{mol}$ = 0.07(±0.01) $(Mor_{1en})^{wor}$ + 69.04	$(Mor_{1en})^{wor}$	3.7 X10^{-10}
21	V_m = 0.17(±0.02) $(Mor_{1p})^{wor}$ + 68.19	$(Mor_{1p})^{wor}$	2.13 X10^{-12}

Inference

In above table the lowest P value (3.06 X10^{-37}) is shown for X^1. So this is selected as most suitable index for prediction of molar refractivity. For this prediction R^2 between observed and predicted $\acute{\eta}_{mol}$ reaches to strongest (0.967) value, pearson product moment correlation constant, r^2 = 0.983, PRESS= 606.333 In the second step two indices considered for regression for which one is X^1 and second is out of rest 20 indices one by one and regression equations were derived with P-values. On the basis of lowest P-value the 2nd most suitable index was selected T(N-S). In third step three variable indices was considered out of which two are X^1 and T(N-S) and third is considered one by one from rest 19 indices. Such process was carried out till 5th step through which 5 indices were selected whose summary given in Table (5). For 6th step when regression was carried out for looking for 6th suitable indices. Then in all regression there was none in which all the six variable shows significant P-values. So, MLR stops till 5 indices and stastistically out of 21 selected indices only five can be used satisfactorily for the prediction of molar refractivity. In Table (5) this is clear that which increasing steps correlation (R^2) is increasing while standard error (SE) and predicted residual sum of squares (PRESS) is decreasing.

Table (5) : Summary of stepwise MLR for prediction of molar refractivity ($\acute{\eta}_{mol}$)

S.No.	Step no.	Developed MLR equation	R^2	PRESS	SE
1	Step-1	$\acute{\eta}_{mol}$= 3.11(±2.97)+7.44(±0.20)χ^1±3.55	0.967	606.33	3.55
2	Step-2	$\acute{\eta}_{mol}$ = 7.04(±0.22)χ^1+ 0.03(±0.01)T(N-S)±6.8	0.973	503.488	3.27
3	Step-3	$\acute{\eta}_{mol}$= 8.28(±0.32)χ^1+ 0.04(±0.01)T(N-S)-0.0 3(±0.01)T(N-O) -6.22	0.982	339.788	2.72

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Impact Factor- 5.070

4	Step-4	$\acute{\eta}_{mol}$ = 8.11(±0.32)χ^1+ 0.06(±0.01)T(N-S)-0.0 3(±0.01)(N-O)+ 0.01(±0.003)$(Mor_{1u})^{wox}$-8.88	0.983	304.076	2.60
5	Step-5	$\acute{\eta}_{mol}$ = 8.05(±0.30)χ^1+ 0.06(±0.01)T(N-S)-0.03 (±0.01)T(N-O)+0.01(±0.004)$(Mor_{1u})^{wox}$-0.17 (±0.07) $(S_s)^{wox}$-1.05	0.985	271.585	2.48
6	Step-6	No variable can be added further satisfactory since in this step each regression equation contains one or more independent variable parameter's p-value > 0.05			

III. RESULTS AND DISCUSSIONS

On the basis of above regression following model can be derived for molar refractivity in terms most significant indices:

$$\acute{\eta}_{mol} = -1.05+8.05(\pm0.30)\ \chi 1 + 0.06(\pm0.01)\mathbf{T(N\text{-}S)} - 0.03(\pm0.01)\mathbf{T(N\text{-}O)}+0.01(\pm0.004)(Mor_{1u})^{wox}-0.17(\pm0.07)\ (S_s)^{wox} \pm 2.48 \quad \rightarrow (5)$$

Statistics of the developed model are as follows:

N	R^2- Adjusted	R^2	Pearson's r	F-ratio	Overall Significance-F	SE	PRESS
50	0.984	0.985	0.993	587.986	$4.24X10^{-39}$	2.48	271.585

$$(\acute{\eta}_{mol})_{predicted} = 0.985(\acute{\eta}_{mol})_{observed} + 1.667 \quad \rightarrow (6)$$

Table (6) :Observed and predicted molar refractivity

Molecular Set	Observed $\acute{\eta}_{mol}$	Predicted $\acute{\eta}_{mol}$	Molecular Set	Observed $\acute{\eta}_{mol}$	Predicted $\acute{\eta}_{mol}$
C_1	76.79	77.44	C_{26}	109.5	110.23
C_2	90.94	90.65	C_{27}	95.53	95.56
C_3	85.01	85.31	C_{28}	94.14	92.88
C_4	100.53	102.43	C_{29}	121.17	123.22
C_5	91.78	92.59	C_{30}	124.60	126.52
C_6	89.61	88.62	C_{31}	156.27	151.96
C_7	94.53	90.12	C_{32}	94.49	94.14
C_8	121.31	121.23	C_{33}	122.09	124.43
C_9	100.11	99.01	C_{34}	135.56	134.25

C_{10}	113.19	113.41	C_{35}	105.95	106.39
C_{11}	95.07	95.36	C_{36}	100.49	101.15
C_{12}	116.91	114.64	C_{37}	114.28	117.35
C_{13}	108.77	105.04	C_{38}	114.52	116.64
C_{14}	98.73	99.91	C_{39}	126.65	128.92
C_{15}	109.76	110.86	C_{40}	125.23	125.37
C_{16}	108.91	109.15	C_{41}	140.22	140.30
C_{17}	98.11	97.20	C_{42}	90.07	90.84
C_{18}	126.33	120.06	C_{43}	129.96	130.51
C_{19}	101.73	102.85	C_{44}	130.41	130.56
C_{20}	96.66	103.36	C_{45}	105.6	106.36
C_{21}	123.08	124.79	C_{46}	161.1	166.29
C_{22}	114.46	111.81	C_{47}	96.19	96.78
C_{23}	131.49	128.67	C_{48}	158.18	157.32
C_{24}	143.49	140.53	C_{49}	135.01	133.73
C_{25}	120.77	116.39	C_{26}	107.35	109.48

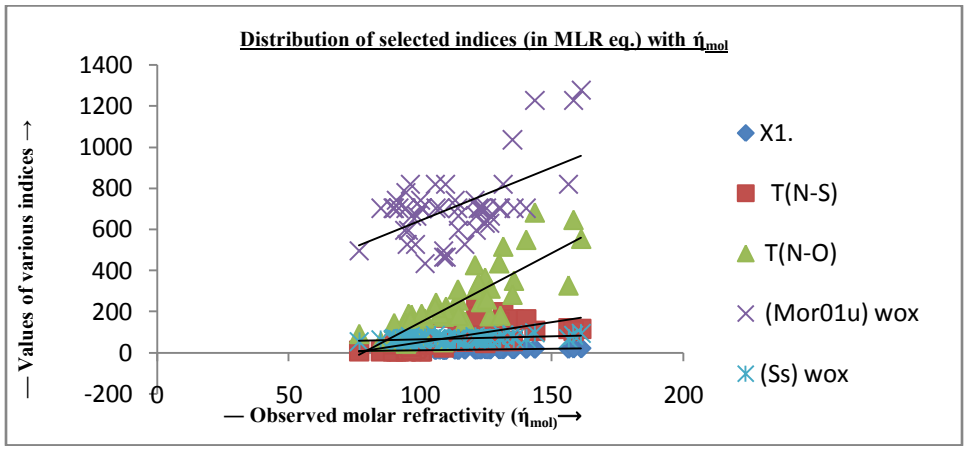

Chart (2): Variation of MLR eq. selectedindices with $\acute{\eta}_{mol}$

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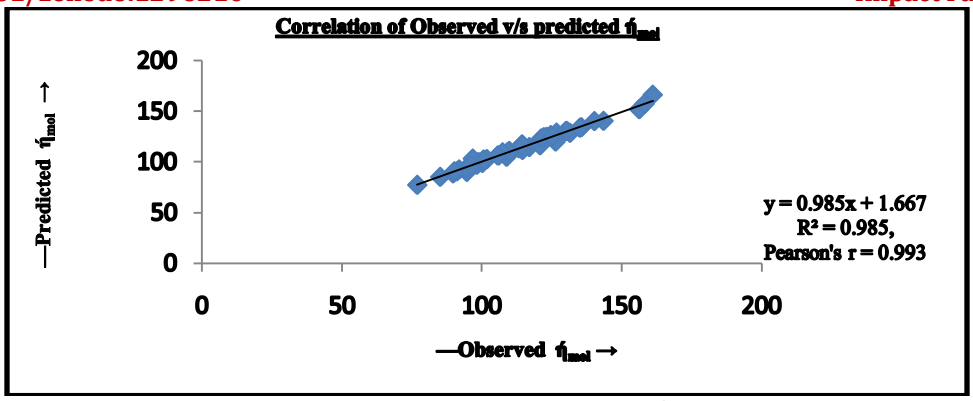

Chart (3): Predicted and observed molar refractivity

IV. CONCLUSION

Molecular Modeling based on molar refractivity

For molar refractivity 50 molecules were applied. The regression equation for prediction of this contains only five indices. Randic index is most potent index since it's coefficient is larger than others. Sum of Keir- Hall topological distances for with out –X group structures also bear moderate predictability. Rest other indices viz. 3D-MoRSE unweighted and calculated for –X group lacking structures, sum of topological distances between nitrogen and oxygen, sum of topological distances between nitrogen and sulphur improves the prediction till some extent due to lower value of regression coefficient.

Molar refractivity is important property for that drugs which are applied as eye drops. So, on the basis of regression equation desired value of refractivity can be introduced in new molecule. Some drugs on dissolution in suitable solvent for preparation of eye drop increases and some decreases the refractive idex of solution. However, refractive index of solution is given by $[(\acute{\eta}_{mol})_{solution} = x_1(\acute{\eta}_{mol})_{solute} + x_2(\acute{\eta}_{mol})_{solvent}]$, So, the drugs (solute) which are applied as eye drop solution, their amount and molar refractivity and solvent molar refractivity should be minimum so that they can minimum affect the refractive index of eye. From equation (6) we know that for minimizing molar refractivity $\chi 1$ should be minimum. Since, $\chi 1$ describe the vertices i.e. shape of molecule so, for reducing $\chi 1$ and hence molar refractivity some has to prefer the insertion of –R and –X group in cephalosporin core structure with less no. of vertices. Further, From the developed regression equation some one can suggest to minimize molar refractivity by insertion of sulphur in –R and –X group should be minimized and oxygen should be preferred because T(N-S) appears in +ive factor and T(N-O) in –ive factor. In the view of 3D-MoRSE –R group is more important because 3D-MoRSE index without –X group $(Mor_{1u})^{wox}$ is in regression equation, so the factors which decrease the 3D-MoRSE index should be introduced in –R group without altering –X group should be introduced. Molar refractivity also play important role in determining the suitability of a drug for oral dose according to Lipinsky's rule of five extension [7]. By this rule, for oral dosesuitability, the drug have to molar refractivity in range 40- 130. For example C_{48}, Cefbuperazone molar refractivity is 158.18 can be minimized by modifying the molecule to P, so that this can be suitable for oral dose.

During the modification toxicity should also be taken in consideration, so, for this purpose regression model derived by R.K. Sharma [8] for median lethal dose (LD_{50}) taken in consideration. The model considered for LD_{50} as follows:

$$\mathbf{LD_{50}}= 56942.16- 1503.32(\pm185.44)\,(Mor_{1en})^{wox}-1062.35\,(\pm152.97)\sum_{u,am,v,en,p}\mathbf{(MoRSE)wox}- 862.25\,(\pm149.06\{\sum_{u,am,v,en,p}\mathbf{(MoRSE)wox}-\sum_{u,am,v,en,p}\mathbf{(MoRSE)wor}\}+ 5070.88(\pm1164.08)\,\mathbf{(N_C)^R}- 1729.42(\pm452.40)\,\mathbf{(S_s)^{wox}}+ 12529.93(\pm3432.91)\,\mathbf{(N_S)^R}+ 29.1140(\pm14.76)\,T(N\text{-}N)\pm 7190 \quad \rightarrow (7)$$

where,$(N_S)^R$= No. of S atoms in group –R

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Table (7) :Comparative data of parental and newer proposed molecule, Pwith improved $\acute{\eta}_{mol}$

S.No.	Name of molecule	(+) ive terms			(-) ive terms		Inference
		$\chi 1$	T(N-S)	$(Mor_{1u})^{wox}$	T(N-O)	$(S_s)^{wox}$	
1	Cefbuperazone (C_{48}) (Parantal molecule)	21.01	108	1225	646	86.50	$\acute{\eta}_{mol}$ ofC_{48}>$\acute{\eta}_{mol}$ ofP_{MR}
2	Proposed molecule, P_{MR}	13.28	44	996	80	80.92	

Table (8) :Comparative data of parental and newer proposed molecule, Pfor toxicity (LD_{50})

S.No.	Name of molecule		(+) ive terms		(-) ive terms				Inference
		$(N_C)^R$	T(N-N)	$(N_S)_R$	$\sum_{u,am,v,en,p}$ (MoRSE)w	(MoRSE)w ox - SUM of 3D (MoRSE)w	$(Mor_{1en})^{wox}$	$(S_s)^{wox}$	
1	Cefbuperazone(C_{48}) (Parantal molecule)	10	294	0	4264	-2051.0	1311.07	86.50	LD_{50} of P_{MR}> LD_{50} ofC_{48}
2	Proposed molecule, P_{MR}	6	3	3	3606.42	-2586.49	1047.63	996	

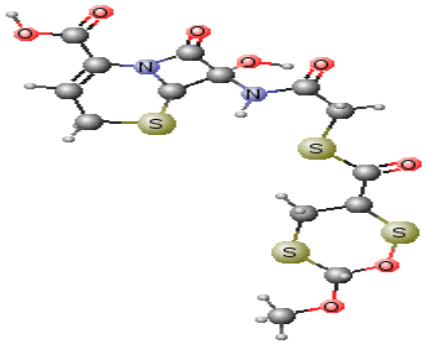

Figure (1) : Proposed molecule, P_{MR} based over reg. eq.(5)

Features of proposed molecule, P_{MR}: This molecule is expected to show lower value of molar refractivity than parental C_{48} (Cefbuperazone), since all the positive terms of reg.eq. (5) are less in Pthan parental C_{48}. However, the less negative value of T(N-O) increases the molar refractivity. But from eq. (5) this is clear that T(N-O) has less predictive power than other (e.g. 1/100 th of $\chi 1$). So the increase in molar refractivity byT(N-O) is negligible than increase made by others e.g. $\chi 1$, T(N-S), $(Mor_{1u})^{wox}$, $(S_s)^{wox}$.Preferred IUPAC Name = (6R,7S)-7-hydroxy-7-(2-{[(3S,6S)-6-methoxy-1,2,5-oxadithian-3-yl]carbonylsulfanyl}acetamido)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylicacid. Particulars of this proposed molecule, P are as follows:
Molecular formula: $C_{14}H_{16}N_2O_8S_4$,
Molecular weight: 468.54,

Value of molar refractivity is 106.97 cm^3, which enable this compound to satisfy the one condition of 'Lipinski's rule of five's extension' as showing suitability for application through oral dose.

Molar volume = 263.1 cm^3, Parachore = 835.9cm^3, Surface tension = 101.9 dyne /cm, polarizability = 42.41, density = 1.78 g/cm^3

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