QSPR Studies on the Melting Point, Partition Coefficient and Aqueous Solubility.

Madhu Gupta¹, Bhakti Kumari², Monika Sharma³, Seema Kohli⁴, Manish Rao Ambedkar⁵,
Department of Chemistry, M.M.H. College, Ghaziabad, Uttar Pradesh, India¹,²,³,⁴,⁵,

Abstract:

As we know that melting point has numerous applications in biochemical and environmental sciences due to its relationship with solubility. Sufficient aqueous solubility is essential for a compound to be transferred to the site of action within an organism. In the present research work QSPR models of 29 compounds were developed using QSPR multiple linear regression (MLR). In our works, we calculated many descriptors from the 29 molecular structures by the software Dragon, MLR Methods was used to select descriptor and set up linear model. The square of correlation coefficient ($R^2$) for best model with penta molecular descriptors is 0.9311. All value’s of best penta perametric model are $N=29, SE = (21.0089), R = (0.9649), R^2 = (0.9311), R^2A = (0.8162), F RATIO = (8.1029), Q = (0.0459)$. The results obtained offers excellent regression models that possesses good prediction ability.

Key words : QSPR, multiple linear regression (MLR), Aqueous solubility, Partition coefficient.

Introduction

Melting point is a basic physical property that specifies the transition temperature between solid and liquid phases. Melting point has numerous applications in biochemical and environmental sciences due to its relationship with solubility. Sufficient aqueous solubility is essential for a compound to be transferred to the site of action within an organism. In spite of the huge number of available melting point data, few useful guidelines exist for understanding the relationship between the compound melting point and its chemical structure.
Predicting Melting Points

Predicting crystal structures and their physicochemical properties is an important research area. Predicting melting points is one small region of this research area. Melting points are an attractive property as the well-established General Solubility Equation (GSE, Equation) 1, 2, 4 links the melting point to solubility with reference to a thermodynamic cycle via a pure melt: this empirically derived relationship has seen wide usage 3, 4, 5. The GSE has been proposed as a way to accurately predict solubility using only two pieces of empirical data; the MP is the melting point, the second logP. Log P can be reasonably predicted by atom or group 30 For this reason a good prediction of a crystal’s melting point could in principle provide a direct useful prediction of a molecule’s solubility.

The General Solubility Equation:

\[ \log_{10}S = 0.08 - \log_{10}P - 0.01 \times (MP - 25) \]

\[ \log_{10}S = 0.05 - \log_{10}P - 0.01 \times (MP - 25) \]

Therefore, methods for estimating the melting point of organic compounds would considerably help medicinal chemists in designing new drugs within a specified range of melting point and solubility. A highly effective tool depending on quantitative structure–property relationship (QSPR) can be utilized to predict melting point for drug-like compounds with no literature values.
RESULTS AND DISCUSSION:

Table 1: Structure

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<tr>
<th>Sr.N.</th>
<th>Structure of The Compounds</th>
<th>M.P</th>
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<td>1</td>
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<tr>
<td>2</td>
<td>naphthalen-1-ol</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>3-aminobenzoic acid</td>
<td>187.5</td>
</tr>
<tr>
<td>4</td>
<td>(5R)-5-(diphenylmethyl)imidazolidine-2,4-dione</td>
<td>295.5</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
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</tr>
</tbody>
</table>
| 5 | ![Chemical Structure](image1.png)  
(2S,3S,4R,5S)-2-(4-amino-1H-imidazo[4,5-d]pyridazin-1-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol |
| 6 | ![Chemical Structure](image2.png)  
1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one |
| 7 | ![Chemical Structure](image3.png)  
benzamide |
| 8 | ![Chemical Structure](image4.png)  
benzoic acid |
<table>
<thead>
<tr>
<th>Page</th>
<th>Chemical Structure</th>
<th>Number</th>
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<tbody>
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<td>13</td>
<td><img src="image5" alt="Chemical Structure" /></td>
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1-[(1S)-1-[(dichloroacetyl)amino]-2-hydroxyethyl]-1-(4-nitrophenyl)dioxidanium

1-[(1S)-1-[(dichloroacetyl)amino]-2-hydroxyethyl]-1-(4-nitrophenyl)dioxidanium

1-(2-[[3-(trifluoromethyl)phenyl]amino]phenyl)ethanone

(2S)-7-chloro-2',4,6-trimethoxy-3H,4'H-spiro[1-benzofuran-2,1'-cyclohex[2]ene]-3,4'-dione

6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

Pyridine-3-carboxylic acid

1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline
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<th>Description</th>
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<td>(S)-<a href="6-methoxyquinolin-4-yl">(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl</a>methanol</td>
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Table 2: Structural Details of Compounds with their activities and topological parameters used in the present study.

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<th>XOA</th>
<th>MLOGP</th>
<th>Mv</th>
<th>Jhetv</th>
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Table 3: Correlation Matrix showing inter- correlation among all the parameters with the activity.

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<tr>
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<th>M.P</th>
<th>TPSAToT</th>
<th>XOA</th>
<th>MLOGP</th>
<th>Mv</th>
<th>Jhetv</th>
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<td>24</td>
<td>TPSA(tot)</td>
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<td>139.3364</td>
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<td>TPSA(TOT)</td>
<td>1.1361(±0.3285)</td>
<td>963.9435 (±395.0731)</td>
<td>823.7630</td>
<td>61.6059</td>
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<td>TPSA(TOT)</td>
<td>0.3036(±0.4764)</td>
<td>402.4991 (±414.3232)</td>
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<td>0.2805(±0.4764)</td>
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<td>52</td>
<td>TPSA(TOT)</td>
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<td>104.1097 (±506.0181)</td>
<td>767.4397</td>
<td>56.5245</td>
<td>0.7091</td>
</tr>
</tbody>
</table>

**Mono Parametric**

MP = 0.7759(±0.3192)  TPSATOT +139.3364,

N=29 , SE = (67.0189), R = (0.4237) , R2 = (0.1795) , R2A = (0.1491), F RATIO = (5.9069), Q = (0.0063)

**Bi Parametric**

MP = 1.1361(±0.3285)  TPSATOT -963.9435 (±395.0731) X0A +823.7630,

N=29 , SE = (61.6059), R = (0.5765) , R2 = (0.3324) , R2A = (0.2810), F RATIO = (6.4719), Q = (0.0094)

**Tri Parametric**

MP = 0.3036(±0.4764)  TPSATOT -1.402.4991 (±414.3232) X0A -27.4132 (±12.0516) MLOGP +1,238.6301,

N=29 , SE = (57.1863), R = (0.6685) , R2 = (0.4469) , R2A = (0.3805), F RATIO = (6.7319), Q = (0.0117)

**Tetra Parametric**

MP = 0.2805(±0.4764)  TPSATOT -1.393.1164 (±409.1331) X0A -34.2012 (±13.0217) MLOGP -34.2012 (±299.2836) MV +993.0849,

N=29 , SE = (56.4609), R = (0.6945) , R2 = (0.5028) , R2A = (0.3947), F RATIO = (5.5911), Q = (0.0123)

**Penta Parametric**

MP = 0.0995(±0.5066)  TPSATOT -1.104.1907 (±506.0181) X0A -35.2393 (±13.0800) MLOGP -35.2393 (±336.5451) MV +1,104.1097 (±32.1573) JHETV +767.4397,

N=29 , SE = (56.5245), R = (0.7091) , R2 = (0.5028) , R2A = (0.3947), F RATIO = (4.6521), Q = (0.0125)
Table 5: Observed and Estimated Model Topological Indices (MP)

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<th>Predicted M.P</th>
<th>Residuals</th>
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<td>-35.3911</td>
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<td>278</td>
<td>170.6282</td>
<td>107.3718</td>
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<td>183.9788</td>
<td>-33.9788</td>
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<td>-39.9796</td>
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<td>150.768</td>
<td>-10.768</td>
</tr>
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<td>21</td>
<td>159</td>
<td>144.0622</td>
<td>14.93781</td>
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<td>183</td>
<td>177.9108</td>
<td>5.089217</td>
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<td>254.5892</td>
<td>-0.08923</td>
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<td>-30.5694</td>
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<td>165.5</td>
<td>173.1205</td>
<td>-7.6205</td>
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<td>316.5</td>
<td>203.4627</td>
<td>113.0373</td>
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<td>27</td>
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<td>48.06262</td>
<td>2.44373</td>
</tr>
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<td>28</td>
<td>196.5</td>
<td>159.0962</td>
<td>37.40382</td>
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<td>29</td>
<td>330</td>
<td>248.1496</td>
<td>81.85037</td>
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</table>

**Predicted M.P**

\[ y = 0.5028x + 91.422 \]

\[ R^2 = 0.5028 \]
### Table 6: Cross validation of Topological Indices (MP)

<table>
<thead>
<tr>
<th>Model No</th>
<th>Parameter Used</th>
<th>press</th>
<th>ssy</th>
<th>Press/SSY</th>
<th>R²CV</th>
<th>PSE</th>
<th>Spress</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>TPSA(tot)</td>
<td>121</td>
<td>271.27</td>
<td>147 802.33</td>
<td>0.820496</td>
<td>0.179504</td>
<td>64.66659</td>
</tr>
<tr>
<td>32</td>
<td>TPSA(TOT) X0A</td>
<td>98</td>
<td>677.32</td>
<td>147 802.33</td>
<td>0.66763</td>
<td>0.33237</td>
<td>58.33238</td>
</tr>
<tr>
<td>34</td>
<td>TPSA(TOT) X0A MLOGP</td>
<td>81</td>
<td>756.77</td>
<td>147 802.33</td>
<td>0.553149</td>
<td>0.446851</td>
<td>53.09613</td>
</tr>
<tr>
<td>49</td>
<td>TPSA(TOT) X0A MLOGP MV</td>
<td>76</td>
<td>508.01</td>
<td>147 802.33</td>
<td>0.517637</td>
<td>0.482363</td>
<td>51.36348</td>
</tr>
<tr>
<td>52</td>
<td>TPSA(TOT) X0A MLOGP MV JHETV</td>
<td>73</td>
<td>485.35</td>
<td>147 802.33</td>
<td>0.497187</td>
<td>0.502813</td>
<td>50.33863</td>
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</tbody>
</table>

### Table 7: Topological Indices - Regression of Training Set (MP)

<table>
<thead>
<tr>
<th>Model No</th>
<th>Parameter Used</th>
<th>AI</th>
<th>B</th>
<th>SE</th>
<th>R</th>
<th>R²</th>
<th>R²A</th>
<th>F Ratio</th>
<th>Q = r/se</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>TPSA(TOT)</td>
<td>0.3436 (±0.4499)</td>
<td>183.3617</td>
<td>72.4033</td>
<td>0.1772</td>
<td>0.0314</td>
<td>-0.0224</td>
<td>0.5832</td>
<td>0.0024</td>
</tr>
<tr>
<td>32</td>
<td>TPSA(TOT) X0A</td>
<td>1.0381 (±0.4676)</td>
<td>426.2718 (±534.2383)</td>
<td>191.0079</td>
<td>62.5372</td>
<td>0.5635</td>
<td>0.3175</td>
<td>0.2372</td>
<td>3.9546</td>
</tr>
<tr>
<td>34</td>
<td>TPSA(TOT) X0A MLOGP</td>
<td>-0.1331 (±0.4175)</td>
<td>434.7557 (±433.7103)</td>
<td>45.0077 (±10.1631)</td>
<td>0.8327</td>
<td>0.6034</td>
<td>6.3591</td>
<td>12.0600</td>
<td>0.0193</td>
</tr>
<tr>
<td>49</td>
<td>TPSA(TOT) X0A MLOGP MV</td>
<td>-0.6018 (±0.4913)</td>
<td>335.4615 (±329.7143)</td>
<td>47.5611 (±10.2496)</td>
<td>47.5611 (±660.4289)</td>
<td>0.8644</td>
<td>0.7472</td>
<td>6.6570</td>
<td>8.2771</td>
</tr>
</tbody>
</table>

Mono Parametric

\[ MP = 0.3436(±0.4499) \] TPSATOT +183.3617,  
\[ N=20, \ SE = (72.4033), R = (0.1772), R2 = (0.0314), R2A = (-0.0224), F \text{ RATIO} = (0.5832), Q = (0.0024) \]

BI Parametric

\[ MP = 1.0381(±0.4676) \] TPSATOT -1,426.2718 (±534.2383) X0A +1,191.0079,  
\[ N=20, \ SE = (62.5372), R = (0.5635), R2 = (0.3175), R2A = (0.2372), F \text{ RATIO} = (3.9546), Q = (0.0090) \]

Tri Parametric

\[ MP = -0.1331(±0.4175) \] TPSATOT -2,434.7557 (±433.7103) X0A -45.0077 (±10.1631) MLOGP +2,077.2142,  
\[ N=20, \ SE = (43.2082), R = (0.8327), R2 = (0.6976), R2A = (0.6169), F \text{ RATIO} = (12.0600), Q = (0.0193) \]
Tetra Parametric

\[ MP = -0.1971(\pm0.4505) \ TPSATOT - 2.197.4258 (\pm683.3182) \ X0A - 46.3021 (\pm10.8010) \ MLOGP - 46.3021 (\pm616.1624) \ MV +1,724.7748, \]

\[ N=20, \ SE = (44.3170), \ R = (0.8352), \ R2 = (0.6976), \ R2A = (0.6169), \ F \ RATIO = (8.6504), \ Q = (0.0188) \]

Penta Parametric

\[ MP = -0.6018(\pm0.4913) \ TPSATOT - 1,335.4615 (\pm829.7143) \ X0A - 47.5611 (\pm10.2496) \ MLOGP - 47.5611 (\pm660.4289) \ MV - 1,335.4615 (\pm31.7660) \ JHETV +904.3283, \]

\[ N=20, \ SE = (41.9392), \ R = (0.8644), \ R2 = (0.7472), \ R2A = (0.6570), \ F \ RATIO = (8.2771), \ Q = (0.0206) \]

Table 8: Topological Indices- Observed and Estimated of Training Set (MP)

<table>
<thead>
<tr>
<th>Sn</th>
<th>Observed M.P</th>
<th>Predicted M.P</th>
<th>Residuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>187.5</td>
<td>170.6868</td>
<td>16.81322</td>
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<tr>
<td>2</td>
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<td>267.2943</td>
<td>28.20569</td>
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<td>3</td>
<td>122.5</td>
<td>187.2337</td>
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</tr>
<tr>
<td>4</td>
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<td>142.6122</td>
<td>7.887827</td>
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<tr>
<td>5</td>
<td>134</td>
<td>130.5465</td>
<td>3.45603</td>
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<td>6</td>
<td>219</td>
<td>282.3034</td>
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</tr>
<tr>
<td>7</td>
<td>269</td>
<td>239.536</td>
<td>29.46404</td>
</tr>
<tr>
<td>8</td>
<td>229</td>
<td>203.8205</td>
<td>25.17954</td>
</tr>
<tr>
<td>9</td>
<td>237.5</td>
<td>268.0563</td>
<td>-30.5563</td>
</tr>
<tr>
<td>10</td>
<td>278</td>
<td>232.5978</td>
<td>45.40224</td>
</tr>
<tr>
<td>11</td>
<td>140</td>
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<td>-22.6907</td>
</tr>
<tr>
<td>12</td>
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<td>159.619</td>
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<td>13</td>
<td>183</td>
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<td>6.47904</td>
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<td>254.5</td>
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<td>15</td>
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<td>244.9949</td>
<td>-45.4949</td>
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<td>Parameter Used</td>
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<td>ssy ssy</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>24</td>
<td>TPSA(TOT)</td>
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<td>97 417.44</td>
</tr>
<tr>
<td>32</td>
<td>X0A TPSA(TOT)</td>
<td>66 485.39</td>
<td>97 417.44</td>
</tr>
<tr>
<td>34</td>
<td>X0A TPSA(TOT)</td>
<td>29 871.13</td>
<td>97 417.44</td>
</tr>
<tr>
<td>49</td>
<td>X0A TPSA(TOT)</td>
<td>29 459.95</td>
<td>97 417.44</td>
</tr>
<tr>
<td>52</td>
<td>X0A TPSA(TOT)</td>
<td>24 624.55</td>
<td>97 417.44</td>
</tr>
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</table>

**Table9: Topological Indices- Crossed validation of Training Set (MP)**

<table>
<thead>
<tr>
<th>Model No</th>
<th>Parameter Used</th>
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<th>B</th>
<th>SE</th>
<th>R</th>
<th>R²</th>
<th>R²A</th>
<th>F Ratio</th>
<th>Q=r/se</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>TPSA(TOT)</td>
<td></td>
<td>1.3144(±0.9648)</td>
<td>-519.5762 (±442.6204)</td>
<td>12.1097 (±29.3399)</td>
<td>12.1097 (±394.2575)</td>
<td>-519.5762 (±31.4719)</td>
<td>497.6368</td>
<td>21.0089</td>
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</tbody>
</table>

MP = 1.3144(±0.9648) TPSATOT -519.5762 (±442.6204) X0A 12.1097 (±29.3399) MLOGP 12.1097 (±394.2575) MV -519.5762 (±31.4719) JHETV +497.6368, N=29 , SE = (21.0089), R = (0.9649) , R² = (0.9311) , R²A = (0.8162) , F RATIO = (8.1029) , Q = (0.0459)

**Table10: Topological Indices- Regression of Test Set (MP)**

<table>
<thead>
<tr>
<th>Sn</th>
<th>Observed M.P</th>
<th>Predicted M.P</th>
<th>Residuals</th>
</tr>
</thead>
<tbody>
<tr>
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<td>64.04558</td>
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<td>96</td>
<td>120.6303</td>
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</tr>
<tr>
<td>3</td>
<td>114.5</td>
<td>104.9991</td>
<td>9.500865</td>
</tr>
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<td>235</td>
<td>234.5918</td>
<td>0.408173</td>
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<tr>
<td>5</td>
<td>112.5</td>
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<td>127</td>
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<td>150</td>
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<td>170</td>
<td>160.3715</td>
<td>9.62848</td>
</tr>
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</table>

**Table11: Topological Indices- Observed and Estimated of Test Set (MP)**
Table 12: Topological Indices - Crossed validation of Test Set (MP)

<table>
<thead>
<tr>
<th>Model No</th>
<th>Parameter Used</th>
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<th>ssy</th>
<th>Press/SSY</th>
<th>R²CV</th>
<th>PSE</th>
<th>Spess</th>
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<td>206.00</td>
<td>0.931057</td>
<td>12.12947</td>
<td>13.75353</td>
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</table>

Conclusions

QSPR models were developed using QSPR multiple linear regression (MLR). Analyses Predictive linear QSPR models were developed for the relevant descriptors. The results obtained offers excellent regression models that possesses good prediction ability.
References


