CHAPTER-3
PARAMETERS USED

3.1 INTRODUCTION:

In the present study we have used topological descriptors as independent parameters for modeling lipophilicity of different molecules in term of log P. Hosoya\(^1\) was the first scientist who used the term topological index (TI) in 1971 for characterizing the topological nature of a graph. TI is an integer very similar to obtain from a graph by the specific recipe. Later on, so many different versions of topological indices have been proposed mostly by the chemists that now days are termed as “topological index” and are used as the general name for these indices. More than one hundred different topological indices are proposed for chemical graphs\(^2-8\).

Topological indices (TIs) are the easy method for translating chemical constitution into numerical values. These values can also be used for correlations with physico-chemical properties or for biochemical quantitative structure-activity-relationships. They are, therefore, scalar numerical descriptors which are now being widely used by theoretical chemists for the characterization of molecular species. The topological method is an exciting new method which is being used to predict how a chemical compound will behave as an effective drug. The method is topological meaning thereby the way the atoms in a molecule are linked. Based on the pattern of linkages, there are various methods through which we can derive a number that characterizes the molecular structure i.e. the topological index\(^9-25\).

During last few decades many works have been published\(^26-33\) which indicate the utility and interest in topological index. The reviews stress the need for new, better topological indices, each with its optimal range of uses. Consequently, today more than four hundred topological indices are known\(^34-51\). A major drawback of most of the topological indices is their degeneracy and two or more values. To overcome this problem new generation topological indices are being derived. Bearing this in mind, highly discriminating distance based topological index J, has been proposed by Balaban\(^52\).
Agrawal & Khadikar\textsuperscript{53-62} have successfully used these topological indices in modeling various toxicities / activities of drug molecules.

### 3.2 DETAILS OF TOPOLOGICAL DESCRIPTORS USED IN PRESENT STUDY:

There are two levels of structural information concerning a molecule. An intermediate level of structural information is the banding or branching pattern in the molecule structure information concerning branching, atom connection, shape and size can be classified under the general term topology, numerous examples; are available illustrating the influence of structure on experimental properties of the molecule. It is found that each property molecular structure, although the nature of this relationship is variable.

A qualification of the topology of molecule which is called molecular connectivity could carry with it sufficient structural information then a close correlation may be possible. A method must develop numerical descriptors encoding within them information relating to the number of atoms and their environment of connectivity. The objective of any such method is the development of structural descriptors. For correlation with properties dependent on molecular connectivity.

The following criteria may be set forth as guidelines in the evaluation of a method for quantization of molecule connectivity.

- The method should make use of simple computations that are not time consuming but readily computerized.
- The method should tend itself to amalgamation with certain indices derived from quantum mechanical approaches such a combination of topological and molecular orbital indices may provide a powerful in the development of SAR (Structure Activity Relationship).
- Numerical descriptor should be unique for given structure.
- The approach should be built fundamentally upon principles of molecule structure rather than upon empirical quantities.
- The method should serve as a basis of structural definition with the capacity for wide application to the many physical, chemical and where possible biological properties.
The topological Descriptors used in the present study are given below:

1. Wiener index (W)
2. Xu index
3. Balaban index (J) & its types
4. Balaban F index
5. Valance Connectivity indices ($^0 \chi_v$ to $^5 \chi_v$)
6. Randic Connectivity indices ($^0 \chi_v$ to $^5 \chi_v$)

### 3.2.1 Wiener Index \(^{63}\) (W):

The Wiener index (W) is the first, oldest, and widely used topological index. Even today it is successfully used in modeling physico-chemical properties as well as biological activities of organic compounds. This index was introduced by Wiener in 1947 and is defined as below. The Wiener index (W) of a graph G is just the sum of distances of all pairs of vertices of G:

\[
W = W(G) = \frac{1}{2} \sum \sum d(v,u|G) \quad \text{..........................(3.1)}
\]

\[
= \frac{1}{2} \sum d(v|G) \quad \text{..........................(3.2)}
\]

where, \(d(v|G)\) is called the distance number of vertex v and is defined\(^84\)

\[
d(v|G) = \sum d(v, u|G) \quad \text{..........................(3.3)}
\]

where, \(n\) is the number of atoms, and \(d\) is the topological distance.

### 3.2.2 Xu Index \(^{64}\):

It is a topological molecular descriptor based on adjacency and distance matrices and is defined as:
Use of Extended Connectivity Index in Drug Designing

\[ Xu = \sqrt[n]{\log L_i = \sqrt[n]{\sum \delta_i \cdot \sigma_j^2} / \Sigma \delta_i \cdot \sigma_j} \] ..............................................................(3.4)

where, ‘n’ is the number of atoms and L represents the valence average topological distance calculated by vertex degree \( \sigma \) and vertex distance degree \( \delta \) of all the atoms. It was proposed as a particularly high discriminate molecular descriptor accounting for molecular size and branching.

3.2.3 BALABAN INDEX (J)\textsuperscript{65}:

It is also called as the Balaban distance connectivity index and symbolized as J. Other names given to this index are distance connectivity index and average distance sum connectivity. It is one of the most discriminating topological index and its values do not increase substantially with molecular size or number of cycles. It is defined in terms of sums over each its row of the distance matrix (D):

\[
J = J(G) \sum (d_i d_j)^{-1/2} \quad \mu + 1 \quad \text{bonds} \] ..............................................................(3.5)

where \( M \) is the number of bonds in a graph \( G \), \( \mu \) is the cyclomatic number of \( G \) and \( d_i \)'s \((i=1,2,3,\ldots,N)\) are the distance sums (distance degrees) of atoms in \( G \) such that

\[
N \quad d_i = \sum (D)_{ij} \quad \mu + 1 \quad \text{bonds} \] ..............................................................(3.6)

\[
j = 1 \]

The cyclomatic number \( \mu \) indicates the number of independent cycles in \( G \) and is equal to the minimum number of cuts (removal of bonds) necessary to convert a polycyclic structure into an acyclic structure:

\[
\mu = M - N + 1 \quad \mu + 1 \quad \text{bonds} \] ..............................................................(3.7)

3.2.4 BALABAN TYPE INDEX \((J_{\text{het}})\) :

This is an extension of Balaban index \((J)\) to molecules containing electro-negativity. In the case of electro-negativity differentiation is made between the atoms of
different kinds by modifying the corresponding elements of the distance matrix $D$. For instance, the following modification was suggested for the diagonal elements:

$$(D)_{ii} = 1 - \left( \frac{Z_c}{Z_i} \right)$$

where $Z_c = 6$ and $Z_i$ is determined by the number of all electrons of atom $i$ or namely $Z_i$ is the atomic number of given elements.

The off-diagonal elements of the modified distance matrix for electro negativity systems are given by the following equation:

$$(D)_{ij} = \sum k_r$$

Where, the summation is over $r$ bonds.

The bond parameter $k_r$ is given by the following expression:

$$k_r = 1/w_r \times \frac{Z_c^2}{Z_i + Z_j}$$

Where, $w_r$ is the bond weight with values of 1, 1.5, 2, and 3 for single, an aromatic, double and triple bond respectively.

### 3.2.5 BALABAN $F^{66}$-TYPE INDEX:

For those properties where not only the “shape” but also the size of graph influences the property or activity, other Balaban index $F^{67}$ has been developed. It defines as:

$$F = J(R+1) = \sum_{\text{all edges}} [d_i \cdot d_j]^{-\gamma}$$

Where, $J$ is Balaban index and $R$ is cyclomatic number, this index is able to separate graph size, cyclicity and branching. For the calculation of Balaban index ‘$J$’ and cyclomatic number ‘$R$’ following expressions were used.

### 3.2.6 KIER AND HALL VALENCE CONNECTIVITY INDICES$^{68}$:

In an attempt to include multiple bonds and hetero atoms in the Randic index and Kier and Hall proposed the valence values of atoms according to the following equation:
\[ \delta_i^v = Z^v - h_i \]                  \hspace{1cm} \text{(3.12)}

where \( Z^v \) is the number of valence electrons of atom \( i \) and \( h_i \) is the number of hydrogens bonded to it. Thus, the Randic connectivity index was modified by Kier and Hall replacing \( \delta_i \) with \( \delta_i^v \).

Randic / Kier / Hall approach has been applied successfully to variety of physicochemical and biological activities. In the molecular connectivity approach, the molecule, as usual, is represented by the hydrogen-suppressed graph. The key feature in the quantization of the hydrogen suppressed graph. The key feature in the quantization of the graph is the characterization of the atom in the molecular skeleton. The molecular connectivity method explicitly introduces the electronic character of atoms into the graphic representation of molecules. Atom identity is specified through the molecular connectivity delta values The simple delta, \( \delta \) and the valence delta, \( \delta^v \).

The simple delta value for a skeleton atom is the number of skeletal neighbours which is equivalent to the vertex degree as used in graph theory however, Kier and Hall have pointed out that this defined graph theory quantity number of skeletal neighbour’s has a direct electronic interpretation. The number of skeletal bonds to a vertex (skeletal atom) is equal to the number of electrons (from that skeletal atom) assigned to sigma type orbital less the number of electrons assigned to sigma bonds to hydrogen atoms .

\[ \delta_i = \text{number of skeletal neighbour of atom } i \]
\[ \delta_i = \sigma_i - h_i \]
\[ \sigma_i = \text{number of atoms } i \text{'s electrons in sigma orbital.} \]
\[ h_i = \text{number of hydrogen atoms bonded to skeletal atoms } i \]

Accordingly, this simple graph quantity I conferred with chemical electronic meaning and the chemical graph theory is born. To increase significantly the amount of electronic information, Kier and Hall developed the valence delta value for explicit encoding of atom identity along with bonding environment and the number of bonded hydrogen.

For atom identity all the valence electrons must be counted, not just these involved in skeletal bonding. For first row atoms in covalent molecules, the valence data for atom \( i \), \( \delta_i^v \), is:
\[ \delta_i^V = z_i^V - h_i \] .................................................................(3.13)

where, \( z_i^V \) = the number of valence electrons for skeletal atom \( i \).

Atoms could be identified by their atomic symbols but such identification is a name or identification tag that bears no direct relation to electronic properties.

In the valence delta value, the atom is identified implicitly along with its immediate bonding environment. In this way although chemical graph theory uses the hydrogen –suppressed graph, the hydrogen atom count is included for the use of the delta values.

For atoms beyond fluorine, the principal difference among family members is the number of core electrons. The valence delta value must explicitly take this factor \( z-z \) into account here \( z \) is the atomic number.

\[ \delta^V = Z^V - h / Z - Z^V - 1 \] .................................................................(3.14)

Thus for a given atom the valence delta takes into account the number of valence electrons and the number of core electrons.

The pair of delta values is seen as a characterization of the atom in its valence state. The simple delta describes the role of atom in the skeleton in terms of its connectiveness and count of sigma electrons; it could be called the sigma electron descriptor. The valence delta, \( \delta^V \), encode the electronic identity of atom in terms of both valence electron count and core electron count. It could be called the valence electron descriptor. The isolated unbounded atom may be thought of as characterized by its atomic number, \( Z \) and the number of valence electrons, \( Z^V \). In its valence state, the bonded atom is characterized by \( \delta \) and \( \delta^V \). Embedded in the molecular skeleton, the full characterization of the atom in the environment of the whole molecule is given by the topological equivalence value.

### 3.2.7 RANDIC CONNECTIVITY INDEX:

The first genuine degree-based topological index was put forward in 1975 by Milan Randic in his seminar paper\(^{69}\) “On characterization of molecular branching”. His index was defined as
with summation going over all pairs of adjacent vertices of the molecular graph G. Randic himself named it “branching index”, After the sometime re-named it as “connectivity index”. Nowadays, commonly refer to it was to the “Randic index”.

With the molecular connectivity $\chi$ proposed by Milan Randic, topological indices began to be used for many quantitative structure-activity-relationships (QSARs) in drug design and the search for new pharmaceuticals. The methodology used by Randic is:

$$\chi = \sum \text{alledges} [\delta_i, \delta_j]^{-1/2}$$ …………………………………………………………(3.16)

Analogous of $\chi$ were developed by Kier and Hall using products of vertex degree for other path that edges i.j. The average distance based Connectivity index, which is often called extended connectivity index J, was introduced by Balaban.

The Balaban $J$ index uses distance sum instead of vertex degrees and is averaged by the number ‘e’ of edges and by the cyclomatic number $R$ defined as :

$$R = E-N+1$$ …………………………………………………………(3.17)

Where $E$ and $N$ are the number of edges and vertices is a graph $G$.

3.3 OTHER INDICATOR PARAMETERS:

Indicator variables (parameter), sometimes called dummy variables or de novo constants are used in multiple linear regression analysis to account for certain features which cannot be described by continuous variables. In QSAR equations they normally describe a structural element, be it a substituent or another molecular fragment. Free Wilson analysis may be interpreted as a regression as a regression analysis approach using only indicator variables. Indicator parameters take only two values, zero & one. Particular class (category) of compound in a given series of drug. They account for the abrupt increase or decrease of a given pharmacological activity at any specific site in drug molecule. Following Indicator parameters are used in present study.

1. Indicator parameter $I_1$ for Halogen groups (R-X)
2. Indicator parameter $I_2$ for Alcohol groups (R-OH)
3. Indicator parameter $I_3$ for Amine groups (R-NH$_2$)
In the present study total 381 chemical compounds are taken from the literature. All the compounds have classified into 2 categories.

1. Aliphatic Compounds
2. Aromatic Compounds

In Aliphatic compound series 161 molecules are included, and in Aromatic compounds 220 molecules are included.

At very first, we have drawn the structure of all the 381 chemical compounds by using ACD Lab Software and Chem.Sketech Software. Here, we used 2D topological descriptor i.e. the representation of molecule considers how the atoms are connected. It defines the connectivity of atoms in the molecule in terms of the presence and nature of chemical bands.

For the present study we calculate the topological descriptors, valance connectivity indices, Randic connectivity indices, Balaban types Index and other Indicator parameters. These descriptors are calculates by using the DRAGON software. The parameter as follows and discussed below:

### TABLE NO. 3.1 TOPOLOGICAL DESCRIPTORS:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Meaning of Indices</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wiener index</td>
<td>$W$</td>
</tr>
<tr>
<td>2</td>
<td>Xu index</td>
<td>$\chi_u$</td>
</tr>
<tr>
<td>3</td>
<td>First Zagreb index $M_1$</td>
<td>$ZM_1$</td>
</tr>
<tr>
<td>4</td>
<td>Second Zagreb index $M_2$</td>
<td>$ZM_2$</td>
</tr>
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</table>

### TABLE NO. 3.2 VALENCE CONNECTIVITY INDEX:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Meaning of Indices</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Valence Connectivity Index Chi-0</td>
<td>$^0\chi^v$</td>
</tr>
<tr>
<td>2</td>
<td>Valence Connectivity Index Chi-1</td>
<td>$^1\chi^v$</td>
</tr>
<tr>
<td>3</td>
<td>Valence Connectivity Index Chi-2</td>
<td>$^2\chi^v$</td>
</tr>
<tr>
<td>4</td>
<td>Valence Connectivity Index Chi-3</td>
<td>$^3\chi^v$</td>
</tr>
<tr>
<td>5</td>
<td>Valence Connectivity Index Chi-4</td>
<td>$^4\chi^v$</td>
</tr>
<tr>
<td>6</td>
<td>Valence Connectivity Index Chi-5</td>
<td>$^5\chi^v$</td>
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</table>
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**TABLE NO. 3.3 RANDIC CONNECTIVITY INDEX :**

<table>
<thead>
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<th>S. No.</th>
<th>Meaning of Indices</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Randic Connectivity Index Chi-0</td>
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<td>Randic Connectivity Index Chi-3</td>
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<td>$\chi^4$</td>
</tr>
<tr>
<td>6</td>
<td>Randic Connectivity Index Chi-5</td>
<td>$\chi^5$</td>
</tr>
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</table>

**TABLE NO. 3.4 BALABAN J-TYPE INDEX :**

<table>
<thead>
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<th>S. No.</th>
<th>Meaning of Indices</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Balaban distance connectivity index</td>
<td>$J$</td>
</tr>
<tr>
<td>2</td>
<td>Balaban-type index from Z weighted distance matrix</td>
<td>$J_{het\ Z}$</td>
</tr>
<tr>
<td>3</td>
<td>Balaban-type index from mass weighted distance matrix</td>
<td>$J_{het\ m}$</td>
</tr>
<tr>
<td>4</td>
<td>Balaban-type index from Van der walls weighted distance matrix</td>
<td>$J_{het\ v}$</td>
</tr>
<tr>
<td>5</td>
<td>Balaban type index from electro-negativity weighted distance matrix</td>
<td>$J_{het\ e}$</td>
</tr>
<tr>
<td>6</td>
<td>Balaban type index from polarizability weighted distance matrix</td>
<td>$J_{het\ p}$</td>
</tr>
<tr>
<td>7</td>
<td>Balaban type index</td>
<td>$F$</td>
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</tbody>
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**TABLE NO. 3.5 OTHER INDICATOR PARAMETERS :**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Meaning of Indicator Parameters</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Indicator – 1 representing Halogen Compounds</td>
<td>$I_1$</td>
</tr>
<tr>
<td>2</td>
<td>Indicator – 2 representing Alcoholic Compounds</td>
<td>$I_2$</td>
</tr>
<tr>
<td>3</td>
<td>Indicator – 3 representing Amine Compounds</td>
<td>$I_3$</td>
</tr>
</tbody>
</table>
REFERENCES:


72. ACD / Lab Software : (11.01 Version) [www.acdlabs.com](http://www.acdlabs.com)

73. Chem.Sketech Software (Version 2015 Freeware)

74. DRAGON Software. (Version 5.0 – 2004, No. of descriptors 1630)