CHAPTER-16

SUMMARY AND CONCLUSION
The need for ongoing development of new drugs needs no emphasis in light of the current global situation of health and disease. Traditionally, the design of novel drugs has essentially been a trial-and-error process despite the tremendous efforts devoted to it by pharmaceutical and academic research groups. It is estimated that only one in 5,000 compounds investigated in preclinical discovery research ever emerges as a clinical lead, and that about one in 10 drug candidates in development ever gets through the costly process of clinical trials. For each drug, the investment may be on the order of $600 million over 10-15 years from its first synthesis to FDA approval. In 2000, U.S. pharmaceutical companies spent more than $22 billion in research and development, which, after inflation adjustment, represents a four-fold increase from the corresponding figure some 20 years ago. In an attempt to counter these rapidly increasing costs associated with the discovery of new medicines, revolutionary advances in basic science and technology are reshaping the manner in which pharmaceutical research is conducted.

The shortcoming of traditional drug discovery as well as the allure of a more deterministic approach to combating disease has led to the concept of "Rational drug design". Nobody could design a drug before knowing more about the disease or infectious process than past.

Modern approaches to computer-aided molecular design fall into two general categories. The first includes Structure-based methods which utilize the three-dimensional structure of the ligand-bound receptor. Many innovative algorithms have been developed and implemented to construct de novo ligands that fit the receptor binding-site in a complementary manner. For "rational" design, the first necessary step is the identification of a molecular target critical to a disease process or an infectious pathogen. Then the important prerequisite of "drug design" is the
determination of the molecular structure of target, which makes sense of the word "rational". In fact, the validity of "rational" or "structure-based" drug discovery rests largely on a high-resolution target structure of sufficient molecular detail to allow selectivity in the screening of compounds.

The second approach includes ligand-based methods in which the physicochemical or structural properties of ligand molecules are characterized. A classic example of this concept is a quantitative structure-activity relationship (QSAR) model, which grants a theoretical ground for lead optimization.

Rational molecular design includes molecular modeling, quantitative structure-activity relationships (QSAR) and quantum mechanical approaches. In drug discovery the characterization of chemical structures in terms of their potential pharmacophoric action is a central issue in the computer-aided search for new leads.

In general, rational drug design assumes the existence of known active compounds with well defined structures. The above methods are then used as a basis for design of known active compounds with enhanced biological activity. Structure-activity-relationships (SARs) are models, which attempt to relate certain structural aspects of molecules to their physicochemical/biological/toxicological properties.

One major emphasis in the SAR methodology is the development of easily calculable parameters, which are available for any arbitrary structure. In QSAR approaches, such as linear free-energy-related (LEFR) approach, either properties (e.g. hydrophobicity) or parameters derived from experimental properties (e.g., electronic, steric, hydrogen-bonding substituent constants) are used as descriptors. The relationship between such properties or property-based descriptors and structure is not always clear.424
Other descriptors are purely structural or nonempirical in the sense that they do not require the input of any experimental data apart from molecular structure and can be calculated directly from the structure of molecules using computer algorithms. Such descriptors have the advantage of being calculated quickly and are available for any molecular structure, real or hypothetical. The major classes of nonempirical molecular descriptors fall into three categories: topological (topostructural, TS; topochemical, TC), geometrical (three-dimensional, 3D), and quantum chemical (QC, both semiempirical and *ab initio*).

The topostructural descriptors quantify information strictly about the adjacency and topological distance between atoms within a molecular structure, while topochemical descriptors encode information about molecular topology and information about the chemical nature of the atoms and bonds within a molecule. From the viewpoint of the demand on computational resources, theoretical molecular descriptors can be ordered as follows:

\[ \text{TS} \ll \text{TC} \ll \text{3D} \ll \text{semiempirical QC} \ll \text{ab initio QC} \]

The TS and TC indices are used first, as they can be calculated most quickly.\(^{424}\)

*Molecular topology overcomes the inherent problem in structure activity relationship (SAR) studies with regard to quantification of chemical structures by translation of chemical structures into characteristic numerical descriptors.* The structure of a molecule can be looked upon as the mode of organization of an assembled entity where some parts (e.g. atoms or atomic cores, more correctly) are involved in a binary relationship: any two atoms, X and Y, in a molecule are either bonded or not bonded. Such a binary relationship, depicting the basic connectivity of atoms in molecules, is satisfactorily represented by a graph \( G = (V, R) \), where the nonempty vertex set \( V \) symbolizes the set of atomic cores and the set \( R \) (often called
the edge set, E) represents the set of chemical bonds. Graphs can be analytically represented by matrices from which a single topological index (TI) or a set of them can be derived. TIs are sensitive to such structural features as size, shape, bond order, branching, cyclicity, neighborhood patterns of atoms and other structural characteristics that are important in predicting chemical behavior. These indices, whether are well chosen are thus a good characterization of the molecular structure.

Although a large number of topological indices of diverse nature have been reported in literature but only a handful of them have been successfully employed in structure activity relationship studies. There is a strong need to develop novel topological descriptors with high discriminating power and low degeneracy for structure activity/property relationship studies so as to facilitate drug design.

1. Development of novel distance based topological descriptors: High discriminating power and absence of degeneracy are the two prerequisites which an ideal topological descriptor must meet and which the theoretical researchers are trying to achieve. In the present study, three novel distance-based topological descriptors have been conceptualized, which take eccentricities of the adjacent vertices into consideration.

Supereccentricity index, a novel distance based topological descriptor represented by \( \xi \) is defined as the summation of the product of the eccentricities of the adjacent vertices for all the vertices in a hydrogen suppressed graph.

Modifications of supereccentricity index were carried out in order to minimize the values of the descriptor to a significantly smaller number in case of larger structures. These modified indices were named as supereccentricity index 1 \( \xi_1 \) and supereccentricity index 2 \( \xi_2 \). Discriminating power and degeneracy of all three novel distance based topological descriptors were investigated using all possible structures.
with 3, 4, 5, and 6 vertices and compared with that of the well-known distance based topological descriptor “Wiener index”.

All the three novel distance based topological indices displayed low degeneracy and high discriminating power for structures with four, five and six vertices. This is evident from the results shown in Table 4.3. The ratios of the highest and lowest values of the supereccentricity index calculated for isomers having four, five and six vertices are 4, 8.4 and 3.1 respectively, which are much higher than that of the Wiener’s index. The modified forms of supereccentricity index also showed better results than that of the Wiener’s index. High discriminating power of the supereccentricity index makes it more sensitive to changes in molecular structure than the Wiener index.

Degeneracy is the measure of ability of an index to differentiate between the relative positions of atoms in a molecule. The supereccentricity index exhibited very low degeneracy for all possible structures having five and six vertices in comparison to the Wiener’s index. Supereccentricity index had only 05 same values out of 21 structures with five vertices and 12 out of 38 structures with six vertices, whereas the Wiener index has 11 same values out of 21 structures with five vertices and 24 out of 38 structures with six vertices.

The modified form, supereccentricity index1 possessed extremely low degeneracy for all structures with 4, 5, and 6 vertices. This is exemplified from the results in the Table 4.3 that for structures with 4 vertices it had no structures with same value. For vertices with 5 and 6 vertices it had 02 same values out of 21 and 03 out of 38 values respectively.
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Presence of low degeneracy at this level simply indicates exceptionally high ability of these indices to differentiate and demonstrate slight variations in the molecular structure mainly branching.

The utility of these novel distance based topological indices for SPR/SAR studies was investigated by carrying out the prediction of physical properties of diverse nature and comparison of their discriminating power was carried out with that of Wiener's index.

To obtain the quantitative structure property relationships of supereccentricity index and its modified forms with various physical properties, the data of boiling points of a group of 62 alcohols, cavity surface areas of a group of 50 alcohols, boiling points of 34 primary and secondary amines and molar refractions of a group of 48 heterogeneous compounds comprising of ethers, amines and alcohols was non-linearly regressed. The QSPR models developed by using these indices were compared with that of the Wiener's index. The average errors were calculated from the experimental and predicted values for all the datasets.

Regression coefficient values of 0.89 to 0.97 were obtained in the datasets using supereccentricity index, which were superior to that of the Wiener's index except in case of the prediction of molar refraction of heterogeneous compounds. Correlation percentages ranging from 94% to ~99% were obtained using supereccentricity index, which were higher than that of Wiener's index.

The high values of regression coefficients, correlation coefficient values and low average errors clearly indicate the high predicting ability of the newly proposed indices over Wiener index.

Simplicity, ease of calculation, high discriminating power, excellent correlation coefficient and regression coefficient values and also very low degeneracy
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of the proposed indices renders the novel distance based topological indices i.e. supereccentricity index, supereccentricity index1 and supereccentricity index2 as promising tools for QSPR/QSAR studies.

2. Development of novel adjacency-cum-distance based topological descriptors:

Adjacency-cum-distance based topological descriptors take into consideration the distance matrix as well as the adjacency matrix. The indices which have been conceptualized in the present study are based on the eccentricity—a parameter obtained from the distance matrix and the degrees of the vertices—a parameter obtained from the adjacency matrix of a hydrogen suppressed molecular graph.

Supereccentric connectivity index is defined as the summation of the square roots of the quotients of the product of eccentricities of adjacent vertices and degree of the concerned vertex, for all vertices in a hydrogen suppressed molecular graph.

Other adjacency-cum-distance based novel indices which have been conceptualized in the present study include super eccentric connectivity index1 \( \xi_1^c \), super eccentric connectivity index2 \( \xi_2^c \), super eccentric connectivity index3 \( \xi_3^c \), super eccentric connectivity index4 \( \xi_4^c \), super eccentric connectivity index5 \( \xi_5^c \). Discriminating power and degeneracy of all the six novel adjacency-cum-distance based topological descriptors were investigated using all possible structures with 3, 4, 5, and 6 vertices and compared with that of the well-known distance based index “Wiener index” and also with adjacency-cum-distance based topological descriptor “eccentric connectivity index”.

All the six novel adjacency-cum-distance based topological indices displayed low degeneracy and high discriminating power for structures with four, five and six
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vertices when compared to that of Wiener's index and eccentric connectivity index.
This is evident from the results shown in Table 4.4.

The ratios of the highest and lowest values of the supereccentric connectivity index calculated for isomers having three, four and five vertices are 1.6, 2.7 and 3.8 respectively which are much higher than that of the Wiener's index as well as eccentric connectivity index. The proposed index also exhibited very low degeneracy for all possible structures with 3, 4, 5 and 6 vertices in comparison to the Wiener's index as well as eccentric connectivity index. Super eccentric connectivity index had only 02 same values out of 21 structures with five vertices and only 03 same values out of 38 structures with six vertices.

Supereccentric connectivity index displayed highest discriminating power among all the novel adjacency-cum-distance topological indices. The values obtained are 4, 15.9, 39.5, and 4 for the structures having three, four, five and six vertices respectively which are far higher than that of the Wiener's index and eccentric connectivity index. Also supereccentric connectivity index had a very low degeneracy i.e. no same values out of 06 structures for four vertices. For structures with five and six vertices also, it displayed very low degeneracy in comparison to Wiener's index and eccentric connectivity index.

The quantitative structure property relationship of the super eccentric connectivity index was investigated with regard to various physical properties, for datasets comprising of primary amines, secondary amines and alcohols etc. Values of Wiener's index and supereccentric connectivity index of all the compounds in various datasets were computed using an in-house computer program. The results obtained by applying the Non-linear regression analysis were far better when compared to the linear regression analysis. Regression coefficient values of 0.90 to 0.97 were obtained.
in datasets using supereccentric connectivity index, which were superior to those of Wiener's index except in case of prediction of molar refraction of mixed compounds. However the proposed index had a significant regression coefficient value. Correlation percentages ranging from 94% to ~99% were obtained using super eccentric connectivity index, which are more than that of Wiener's index.

High values of regression coefficients, correlation coefficient values, low average errors, high discriminating power and low degeneracy clearly indicate the high predicting ability of the newly proposed adjacent-cum-distance based indices over Wiener index.

Present studies proved that these novel adjacency-cum-distance based topological descriptors offer vast potential for QSPR/QSAR studies.

3. Prediction of biological activities of diverse nature using topological indices:

It is clearly evident from the review of literature that topological indices are widely used in predicting the physicochemical properties and biological activities of diverse nature of chemical classes. Keeping same in view, the different topological descriptors like Wiener's index, molecular connectivity index, Zagreb group parameters, eccentric connectivity index, superadjacency index, Wiener's topochemical index, atomic molecular connectivity index, superadjacency topochemical index etc. were applied for the prediction of biological activities of different categories of therapeutic compounds like anti-HIV, dopaminergic receptor agonists/antagonists, ACAT inhibitors etc. The values of indices were calculated for each analogue in the dataset using an in-house computer program. Suitable models were then developed after identification of the active ranges by moving average analysis. Subsequently, a biological activity was assigned to each analogue in the
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dataset, which was then compared with the reported biological activity. Investigations revealed significant correlations between the topological indices and biological activity of diverse natures. The predictability of the models was found to vary from 80% to 92% for different classes of compounds.

3.1 Development of models for the prediction of HIV-Protease inhibitory activity of Tetrahydropyrimidin-2-ones:

In 1981, the world was introduced to a lethal killer in our midst that has forever changed the lives of both infected as well as non-infected individuals through its impact on our health, society, and culture. Acquired Immune Deficiency Syndrome (AIDS) is caused by the HIV that has acted as an incredible catalyst for scientific breakthroughs in the attempt to find a cure. The most common form of treatment up to date is Combination Therapy or Highly Active Antiretroviral Therapy (HAART); this method uses a combination of two or more reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs).

The approved HIV-protease inhibitors are based on amino acid sequences recognized and cleaved in HIV proteins. Indinavir, nelfinavir, ritonavir, saquinavir, lopinavir, amprenavir and the most recently approved atazanavir are structurally related molecules. Most contain a synthetic analogue of the phenylalanine-proline sequence at positions 167 and 168 of the gag-pol polyprotein that is cleaved by the protease. However such compounds possess poor pharmacokinetics and are complex and expansive to synthesize. To overcome such difficulties, significant efforts have been devoted to the development and SAR study of non-peptide inhibitors such as cyclic ureas and other heterocycles.

In the present investigations, Wiener’s Index – a distance-based topological descriptor, Zagreb group parameter – an adjacency-based topological descriptor and
eccentric connectivity index – an adjacency-cum-distance based topological descriptor had been used for predicting the HIV-protease inhibitory activity of tetrahydropyrimidin-2-ones by the development of suitable models.

The values of the Wiener’s index, Zagreb group parameter and eccentric connectivity index for each of the 80 analogues comprising the dataset were computed. The dataset was randomly divided into two sets. Compounds having odd serial number were designated as test set and those having even number were separated as training set. Suitable models were developed after identification of the active range by maximization of the moving average with respect to the active compounds (<35% = inactive, 35-65% = transitional, ≥65% = active) in the training set. Subsequently, each analogue in the test set was assigned a biological activity using this model, which was then compared with the reported HIV-protease inhibitory activity. The models were developed using the training set of the compounds and evaluated using the test set. The accuracy of prediction is based upon the compounds in the test set only.

The overall degree of prediction was found to be ~88% in case of Wiener’s index, ~86% in case of Zagreb group parameter, and ~86% in case of eccentric connectivity index. Prediction with the Wiener’s index was better when compared to eccentric connectivity index and Zagreb group parameter. High degree of predictability of the proposed models offer a vast potential for providing lead structures for the development of potent HIV-protease inhibitors.

3.2 Development of models for the prediction of anti-HIV activity of Dihydro (alkythio) (naphthylmethyl) oxopyrimidines:

The enzyme reverse transcriptase of HIV-1 is an essential enzyme required for the catalytic conversion of genomic RNA into double-stranded proviral DNA after
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cell entry by using the RNA- and DNA-dependent polymerase and ribonuclease H (RNase H) activities of the enzyme and therefore is the target for antiviral therapy against AIDS.

This enzyme has been an active target for drug development for a number of years. Many inhibitors of HIV-RT have been discovered, which can be divided into two categories: The first group consists of nucleoside reverse transcriptase inhibitors (NRTIs). These are competitive inhibitors, which act as DNA chain terminators. The others are the non-nucleoside reverse transcriptase inhibitors (NNRTIs). Inhibitors of the latter class are particularly attractive drug candidates because their binding is highly specific to the reverse transcriptase of HIV-1, and therefore, they lead to less adverse side effects. The NNRTIs currently approved for the use in highly active antiretroviral therapy include nevirapine, delavirdine and efavirenz.

Currently approved drugs for AIDS suffer from a number of limitations including limiting site effects and emergence of drug resistant mutants of the virus. Therefore there is a strong need for development of newer potent anti-HIV agents with fewer side effects.

In the present investigations, suitable mathematical models have been developed for the prediction of anti-HIV activity of Dihydro(alkylthio)(naphthylmethyl)oxopyrimidines using Wiener's index—a distance based topological descriptor, molecular connectivity index—an adjacency based topological descriptor and eccentric connectivity index—an adjacency-cum-distance based topological descriptor. Relationship between topological descriptors and anti-HIV activity had been investigated using a dataset comprising of 67 dihydro(alkylthio)(naphthylmethyl)oxopyrimidines analogues. The values of Wiener's index, molecular connectivity index and eccentric connectivity index for each of the
67 analogues in the dataset were computed and suitable models were developed after identification of active ranges by moving average analysis. Subsequently, a biological activity was assigned to each analogue involved in the dataset which was then compared with the reported anti-HIV activity. The values of the Selectivity Index were also calculated for all the ranges of the models using different topological indices.

The overall degree of prediction was found to be 88% in case of Wiener's index, ~89% in case of molecular connectivity index and 86% in case of eccentric connectivity index. The analogues in the active range possessed not only the high anti-HIV activity but also low toxicity. The analogues in the transitional range had a high value of selectivity index, but possessed lower anti-HIV activity.

High degree of predictability of the proposed models based upon the topological indices offer a vast potential for providing lead structures for the development of potent but safe anti-HIV compounds.

3.3 Development of models for the prediction of dopamine receptors binding affinity of $N$-[4-(4-arylpiperazin-1-yl) butyl]aryl carboxamides:

The neurotransmitter dopamine (DA) is critical to many of the vital functions of daily life, including emotional response, the regulation of movement, and the control of cognition, including attention. Neurons responsible for the release of DA project to the cortex, striatum, hypothalamus, and limbic systems of the brain. In humans, diseases like Schizophrenia, Parkinson's disease, and Attention Deficiency Hyperactivity Disorder (ADHD) have all been tied to malfunctioned dopaminergic neurotransmission, thus strengthening the correlation between the role of DA receptors and the regulation of behavior and cognition.
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Dopamine D3 receptors are relatively few in number but display a discrete localization in special limbic areas of the central nervous system, which are thought to control emotional and cognitive but not locomotor functions. A suitable selective dopamine D3 receptor antagonist may provide antipsychotic properties in the relative absence of limiting extrapyramidal side effects. Another therapeutic use of D3 agents is for the treatment of Parkinson’s disease (PD) because dopamine agonists used in PD therapy have, in many cases higher affinity for the D3 receptors.290 Recently the D3 preferring agonists pramipexole and ropinirole have been introduced in therapy for the effective treatment of PD. The D3 receptor subtype would also be involved in the pharmacological effects of psychostimulant drugs.

However the in vivo function of dopamine D3 and D4 receptors and their role in different CNS disorders remains debatable because of the lack of receptor selectivity of the different pharmacological agents.

In the present investigations, mathematical models were developed for the prediction of Dopamine D3 and D4 receptor binding affinity of N-[4-(4-arylpiperazin-1-yl)butyl]aryl carboxamides by using topological indices. These models were based on Wiener’s index-a distance based topological index, molecular connectivity index-an adjacency based topological index and eccentric connectivity index-an adjacency-cum-distance based topological index. The values of Wiener’s index, molecular connectivity index and eccentric connectivity index were calculated for 37 derivatives of N-[4-(4-Arylpiperazin-1-yl)butyl]aryl carboxamide in the dataset and suitable models were developed after identification of active ranges by moving average analysis. Subsequently, a biological activity was assigned to each analogue involved in the dataset which was then compared with the reported dopamine D3 and D4 receptor binding affinity. The overall degree of prediction was found to be 89% in
case of Wiener's index, ~89% in case of molecular connectivity index and 92% in case of eccentric connectivity index with regard to dopamine D₃ receptor binding affinity. With regard to dopamine D₄ receptor, the degree of prediction was found to be 81% in case of Wiener’s index, 79% in case of molecular connectivity index and 81% in case of eccentric connectivity index. Some of the compounds in the active ranges of the models for D₄ receptor binding affinity showed significant D₃ receptor binding affinity.

These models offer a vast potential for providing lead structures for development of therapeutic agents particularly with regard to dopamine D₃ receptor binding affinity.

3.4 Development of models for prediction of Dopamine D₃ receptor binding affinity of N-(ω-(4-(2-methoxyphenyl)piperazin-1-yl)alkyl)carboxamides:

In the present study relationship of Wiener’s Index – a distance-based topological descriptor, Zagreb group parameter – an adjacency-based topological descriptor and eccentric connectivity index – an adjacency-cum-distance based topological descriptor with dopamine D₃ receptor binding affinity of N-(ω-(4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)carboxamides had been investigated. Relationship between topological descriptors and dopamine D₃ receptor binding affinity had been investigated using a dataset comprising of 73 analogues of N-(ω-(4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)carboxamides. Values of all the topological indices were calculated using an in-house computer program and suitable models were developed after identification of active ranges by moving average analysis. Subsequently, a biological activity was assigned to each analogue involved in the dataset which was then compared with the reported dopamine D₃ receptor binding affinity. The overall degree of prediction was found to be 84% in case of Wiener’s
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index, ~87% in case of Zagreb group parameter and 83% in case of eccentric connectivity index with regard to dopamine D$_3$ receptor binding affinity.

Studies reveal that these models offer a vast potential for the design of lead structures for the development of therapeutic agents with D$_3$ receptor binding affinity.

3.5 Development of models for prediction of adenosine receptors binding activity of 4-aminof1,2,4-triazolo[4,3-a]quinoxalines:

Activation of ARs mediates several receptor subtype-specific physiological processes that include cardiac rate, smooth muscle tone, platelet aggregation, inflammation, cell growth and death, and neurotransmission. Adenosine A$_3$ receptor has been reported mostly in brain, lung, liver, heart, kidney, and testis. In the brain, A$_1$ receptors are abundant, especially in the cortex, whereas A$_2$A receptors are mainly located in the striatum. Conversely, both adenosine A$_2$B receptors and A$_3$ receptors are present in low amounts in the brain. Activation of A$_1$ receptors results in the bradycardiac, cerebroprotective and antilipolytic effects of adenosine. Activation of A$_2$A receptors results in the hypotensive and antiplatelet aggregatory effects of adenosine. However, there are not yet any selective ligands with which to characterize physiological effects of selective activation of A$_2$B receptors.

Numerous structurally diverse non-xanthines antagonists have also been identified during the last decade many of which have only poor to moderate affinity. These include the tricyclic non-xanthine antagonists such as triazoloquinazolines, imidazoquinolines and triazoloquinoxalines. Furthermore the role of the adenosine receptor subtypes is still ill-defined. In a search for defining the role of adenosine and adenosine receptors in the brain and other biological systems, there is a strong need for the development of highly selective adenosine receptor agonists and antagonists.
In the present study relationship of Wiener's Index – a distance-based topological descriptor, Zagreb group parameter – an adjacency-based topological descriptor and eccentric connectivity index – an adjacency-cum-distance based topological descriptor with adenosine A₁ and A₂ receptors binding activities of 4-Amino[1,2,4]triazolo[4,3-a]quinoxalines was investigated by the development of suitable models. The values of three topological indices were calculated using an in-house computer program for all the 138 derivatives of 4-Amino[1,2,4]triazolo[4,3-a]quinoxaline in the dataset and suitable models were developed after identification of active ranges by moving average analysis. Subsequently, a biological activity was assigned to each analogue involved in the dataset which was then compared with the reported adenosine A₁ receptor binding activity. Same procedure was repeated for the adenosine A₂ receptor binding activity. The overall degree of prediction was found to be 80% in case of Wiener's index, 81% in case of Zagreb group parameter and 82% in case of eccentric connectivity index with regard to A₁ receptor binding activity. With regard to adenosine A₂ receptor binding activity, the overall accuracy of prediction was found to be 90% in case of Wiener's index, 88% in case of Zagreb group parameter and 89% in case of eccentric connectivity index.

Also the values of all the three topological indices calculated for N⁶-Cyclohexyladenosine, a potent A₁ receptor agonist were found to be present in the predicted active ranges for A₁ receptor binding activity. These models proved to be excellent in predicting the adenosine receptors binding activities. These correlations can easily provide a valuable tool for the development of ideal novel A₁ and A₂ receptor ligands, agonists or antagonists.

3.6 Development of models for the prediction of acyl-coA: cholesterol o-acyltransferase inhibitory activity of (aminosulfonyl) ureas:
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Inhibition of acyl-coA:cholesterol O-acyltransferase (ACAT), the enzyme which catalyses the intracellular formation of cholesteryl esters, is a very attractive target for the treatment of hypercholesterolaemia and atherosclerosis. However, in the past years many ACAT inhibitors gave disappointing results in clinical trials showing very low efficacy. In addition, their development was affected by the adrenotoxicity observed in many compounds. The discovery of two isoforms of the enzyme, namely ACAT1 and ACAT2, with different substrate specificity and different potential function, offers precious information for planning selective inhibitors with reduced secondary effects. Macrophages express predominantly ACAT-1, whereas intestines express predominantly ACAT-2. Human liver express both ACAT-1 and ACAT-2, with a predominance of ACAT-1. Today some potent, bioavailable and non adrenotoxic ACAT inhibitors are under clinical evaluation. Amongst others, a very promising compound is Avasimibe, presently in phase III clinical trials as anti-hyperlipidemic and anti-atherosclerotic agent. Finally, ACAT inhibitors have recently been proposed for the treatment of Alzheimer's disease.

In the present investigations mathematical models had been developed for the prediction of ACAT inhibitory activity of (aminosulfonyl)ureas by using topological indices. These models were based on *Wiener's index*-a distance based topological index, *molecular connectivity index*-an adjacency based topological index and *eccentric connectivity index*-an adjacency-cum-distance based topological index. The values of *Wiener's index, molecular connectivity index* and *eccentric connectivity index* were calculated for all 41 analogues in the dataset using an in-house computer program and suitable models were developed after identification of active ranges by analyzing the resultant data by maximization of the moving average with respect to
active compounds. Subsequently, each analogue was assigned a biological activity which was then compared with the reported *in vitro* ACAT inhibitory activity.

Investigations revealed significant correlations between the topological indices used in the present study and ACAT inhibitory activity of (aminosulfonyl)ureas. The overall degree of prediction was found to be 83% in case of Wiener's index, 86% in case of eccentric connectivity index, and 91% in case of molecular connectivity index. Prediction with the molecular connectivity index was better when compared to Wiener's index and eccentric connectivity index.

High degree of prediction of the proposed models can easily provide valuable lead structures for the development of potent ACAT inhibitors for controlling hypercholesterolemia and atherosclerotic disorders.

### 3.7 Development of models for the prediction of CDK-1 inhibitory activity of aloisines:

Cell cycle progression is tightly controlled by the activity of cyclin-dependent kinases (CDKs). CDKs are inactive as monomers, and activation requires binding to cyclins, a diverse family of proteins whose levels oscillate during the cell cycle, and phosphorylation by CDK-activating kinase (CAK) on a specific threonine residue. For example, cyclins A and B activate CDK1, cyclins A and E regulate the activity of CDK2, and the D-type cyclins are associated with CDK4. The central role of CDKs in cell cycle regulation makes them a promising target for studying inhibitory molecules that can modify the degree of cell proliferation. While the concentration of the CDKs remains relatively constant throughout the cell cycle, cyclin expression and degradation occur in a periodic fashion. The rise and fall of cyclin concentrations are timed to provide specific CDK activities, as they are needed for progression through the various stages of the cell cycle.
The recognition of the importance of CDKs to the process of cell division has stimulated an interest in them as potential targets for proliferative diseases such as cancer, psoriasis, and restenosis, and for the prevention of chemotherapy-associated side effects such as alopecia.

Suitable models were developed for the prediction of CDK-1 inhibitory activity of 6-phenyl[5H]pyrrolo[2,3-b]pyrazines (aloisines) based on the topological indices in the present investigations. Wiener index—a distance-based topological index, Zagreb group parameter—an adjacency-based topological index and eccentric connectivity index—an adjacency-cum-distance-based topological index were used for the correlation of the CDK-1 inhibitory activity. The values of all the three topological indices were computed and suitable models were developed after identification of active ranges by analyzing the resultant data by maximization of moving average with respect to the active compounds. Subsequently, each analogue was assigned a biological activity which was then compared with the reported CDK-1 inhibitory activity.

Models based upon all the three topological descriptors i.e. Wiener's index—a distance-based topological descriptor, Zagreb group parameter—an adjacency-based topological descriptor and eccentric connectivity index—an adjacency-cum-distance-based topological descriptor exhibited high degree of predictability ranging from 82% to 84% with regard to CDK-1 inhibitory activity. Prediction with regard to Zagreb group parameter was better when compared to Wiener's index and eccentric connectivity index. High degree of predictability of the proposed models can easily provide valuable lead structures for the development of potent CDK-1 inhibitors.

3.8 Development of models for the prediction of AT1 receptor binding affinity of 5-[1-(4'-carboxybenzyl)imidazolyl]methylidene] hydantoins:
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The effects of angiotensins are exerted through specific cell surface receptors. Two subtypes of angiotensin receptors have been identified that are now designated as AT₁ and AT₂. Both the AT₁ and AT₂ receptors are members of G protein-coupled receptor family. Most of the biological effects of angiotensin II are mediated by the AT₁ receptor; functional roles for the AT₂ receptor are poorly defined.

Saralasin, a specific Ang II antagonist, lowered blood pressure in patients with elevated renin levels but, in addition, exhibited partial agonist effects in vivo and poor bioavailability. This peptide, however, has served to demonstrate the usefulness of Ang II blockade and hence established several research programs directed toward the discovery of nonpeptide Ang II antagonists. Losartan was the first orally active, potent and selective nonpeptide AT₁ receptor antagonist. Afterwards hundreds of AT₁ receptor antagonists have been synthesized, representing a diverse array of chemical structures.

Relationship of topological indices i.e. Wiener’s Index – a distance-based topological descriptor, molecular connectivity index – an adjacency-based topological descriptor and eccentric connectivity index – an adjacency-cum-distance based topological descriptor with AT₁ receptor binding affinity was investigated by the development of suitable models. Relationship between topological descriptors and AT₁ receptor binding affinity had been investigated using a dataset comprising of 73 analogues of 5-[[1-(4’-carboxybenzyl)imidazolyl] methylidene] hydantoins. The values of all the topological indices were computed for each analogue using an in-house computer program and suitable models were developed after identification of active ranges after analyzing the resultant data by maximization of moving average with the respect to active compounds. Subsequently, each analogue was assigned a biological activity which was then compared with the reported AT₁ receptor binding...
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affinity. Models based upon all the three topological descriptors i.e. Wiener's index - a distance-based topological descriptor, molecular connectivity index – an adjacency-based topological descriptor and eccentric connectivity index – an adjacency-cum-distance based topological descriptor exhibited high degree of predictability ranging from 89% to 92% with regard to AT₁ receptor binding affinity. Prediction with the molecular connectivity index i.e. an adjacency based topological index, was better when compared to Wiener's index and eccentric connectivity index.

High degree of prediction of the proposed models offer a vast potential for providing lead structures for the development of Ang-II specific AT₁ receptor ligands.

3.9 Development of models for the prediction of Neutral Endopeptidase and Angiotensin-Converting Enzyme inhibitory activity of mercaptoacyldipeptides:

Angiotensin Converting Enzyme (ACE) belongs to the enzymatic cascade of the renin-angiotensin system and releases the vasoconstrictor peptide angiotensin II from its inactive precursor angiotensin I. Angiotensin II is further converted in the adrenal gland to angiotensin III. Angiotensin II has vasoconstrictor and sodium-retaining activity. Angiotensin II and III both stimulate aldosterone release leading to increased sodium and water retention and thus high blood pressure.

NEP is an endothelial, membrane-bound zinc metallopeptidase that cleaves endogenous peptides at the amino side of hydrophilic residues. It has a catalytic unit similar to ACE for degradation of a number of endogenous vasodilator peptides, including ANP, BNP, CNP, substance P, and bradykinin as well as vasoconstrictor peptides, including endothelin-1 and angiotensin II. Because of their ability to reduce blood volume and arterial pressure, the inhibitors of NEP are being evaluated as natriuretic-diuretic agents in the treatment of congestive heart failure, hypertension.
Furthermore NEP and ACE are both involved in the inactivation of bradykinin (Bk), a vasodilatatory peptide, at their epithelial and endothelial sites respectively.

The design of dual inhibitors of neutral endopeptidase and angiotensin converting enzyme has become an important therapeutic challenge in the last few years. In order to facilitate the development of NEP and ACE inhibitors, suitable models were developed based on the topological indices for the prediction of NEP and ACE inhibitory activity of mercaptoacyldipeptides.

Topological indices which were used in the present investigations include Wiener's index—a distance based topological index, molecular connectivity index—an adjacency based topological index and eccentric connectivity index—an adjacency-cum-distance based topological index. The values of the topological indices were computed for all 39 analogues in the dataset using an in-house computer program and suitable models were developed after identification of active ranges after analyzing the resultant data by maximization of moving average with respect to active compounds. Subsequently, each analogue was assigned a biological activity which was then compared with the reported NEP and ACE inhibitory activity.

Models based upon all the three topological descriptors i.e. Wiener's index—a distance based topological descriptor, molecular connectivity index—an adjacency based topological descriptor and eccentric connectivity index—an adjacency-cum-distance based topological descriptor exhibited high degree of predictability ranging from 77% in case of Wiener's index, 83% in case of molecular connectivity index and 91% in case of eccentric connectivity index with regard to ACE inhibitory activity. The degree of predictability was found to be higher in case of models based upon eccentric connectivity index. The degree of predictability was found to be 90% in case of Wiener's index, 90% in case of molecular connectivity index and 82% in case of...
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eccentric connectivity index with regard to NEP inhibitory activity. The potency of the active ranges based upon these models was found to be very high.

These models offer a vast potential for providing lead structures for the development of therapeutic agents with regard to NEP and ACE inhibition.

3.10 Development of models for the prediction of GABA-A receptor binding affinity of 3-phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-a]phthalazines:

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the brain. GABA-A receptors also have multiple allosteric modulatory sites for barbiturates, steroid anesthetics, loreclezole, avermectins and benzodiazepines that all modulate opening of the channel through different mechanisms of action. Of these, the benzodiazepine (BZ) site is the best characterized because of its role in mediating the clinical effects of anxiolytics such as diazepam. It has been shown that the benzodiazepine binding site occurs at the interface of the α and γ subunit of the GABA-A receptor, with the pharmacology of the benzodiazepine site being determined by the particular α and γ subunits present. Currently only a limited number of GABA-A subtype selective ligands have been reported. Zolpidem and CL-218,872 have 10- to 20-fold selectivity for α1-over α3-containing subunits.

Currently used anxiolytic benzodiazepines such as diazepam are nonselective, high-efficacy agonists, and these compounds show sedative, muscle-relaxant, and amnesic properties. Zolpidem is a high-efficacy agonist that has selectivity for the α1 subtype (the major subtype of GABA-A receptors in the central nervous system), and it is particularly sedative in animal tests and in man. This suggests that compounds with selectivity for the α2 subtype and/or α3 subtype may retain the desirable anxiolytic activity unselective benzodiazepines but possess an improved side effect profile.
In the present study, relationship of Wiener’s topochemical index—a distance-based topochemical descriptor, atomic molecular connectivity index—an adjacency-based topochemical descriptor and superadjacency topochemical index—an adjacency-cum-distance based topochemical descriptor with the binding affinities of 3-Phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-a]phthalazines to α3 subtype of GABA-A receptor had been investigated. The values of all the topochemical indices were computed and suitable models were developed after identification of active range by maximization of the moving average with respect to the active compounds (<35% = inactive, 35-65% = transitional, ≥65% = active). Subsequently, each analogue was assigned a biological activity using this model which was then compared with the reported binding affinity to α3 subtype of GABA-A receptor. The overall degree of prediction was found to be ~89% in case of Wiener’s topochemical index, ~89% in case of atomic molecular connectivity index and ~82% in case of superadjacency topochemical index. Careful examination of the structure of the compounds in the active range indicates that the substitution at position-6 and 3 of the 3-Phenyl-6-(2-pyridyl)methyloxy-1,2,4-triazolo[3,4-a]phthalazine is most critical for activity.

The results obtained from mathematical models based on Wiener’s index, molecular connectivity index, superadjacency index and eccentric connectivity index were not found to be significant. No active range was identified from the models based on these indices.

High degree of predictability of the proposed models based upon the topochemical indices offer a vast potential for providing lead structures for the development of potent ligands with high affinity to α3 subtype of GABA-A receptor.

3.11 Development of models for the prediction of MRP1 inhibitory activity of pyrrolopyrimidines and templates derived from pyrrolopyrimidine:
The appearance of tumor cells resistant to a range of cytotoxic drugs is a serious problem in cancer chemotherapy. This phenomenon is called multidrug resistance (MDR). The multidrug resistance-associated proteins (MRPs) are a subfamily of the ATP-binding cassette transport protein family involved in drug resistance and excretion of organic anions. MRP1 transports drugs conjugated to the anionic ligands glutathione (GSH), glucuronide, or sulfate or transports them in an unmodified form, probably together with GSH. MRP1 can transport many exogenous agents, such as chemotherapeutics (daunorubicin, etoposide and vincristine), metalloid salts (antimony and arsenic) and aflatoxin B1. MRP1 also transports endogenous compounds such as arachidonic acid derivatives, LTC4 (leukotriene C4) is the highest affinity substrate, glutathione conjugates, glucuronide and sulphate conjugates of bile salts, 17β-oestradiol 17-(β-D-glucuronide) and bilirubin glucurononides.

Multidrug resistance mediated by multidrug-resistance-associated protein remains a major obstacle for the successful treatment of cancer. Inhibition of MRP1 transport is important for high efficacy of anticancer drugs. The development of specific MRP1 inhibitors is still in its infancy. In order to develop new MRP1 inhibitors, relationship of topological indices and MRP1 inhibitory activity of pyrrolopyrimidines had been investigated in the present studies.

For establishing the correlation with MRP1 inhibitory activity, the three topological indices i.e. Wiener’s index, molecular connectivity index and eccentric connectivity index were computed and suitable models were developed after identification of active ranges by maximization of the moving average with respect to the active compounds. Subsequently each analogue was assigned a biological activity which was then compared with the reported MRP1 inhibitory activity.
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The overall accuracy of prediction of the proposed model based upon Wiener's index was found to be 88%. The results obtained from the models based upon molecular connectivity index and eccentric connectivity index were not found to be significant. High degree of predictability of the model based upon Wiener's index offers a vast potential for providing lead structures for the development of potent MRP1 inhibitors.

Investigations pertaining to the predictability of the models based upon topological indices for diverse nature of therapeutic agents clearly indicate the vast potential of the topological indices for drug design. High degree of predictability, high accuracy of prediction, high potency of the active ranges and simplicity of the mathematical models developed using topological indices for various diseases like AIDS, Schizophrenia, Alzheimer’s disease, cancer, psychological disorders, resistance to chemotherapy, identification of receptors of different categories, for prediction of physical properties like boiling points and for determining physicochemical properties like molar refraction help in development of lead structures and thus important tools for rational approach to drug design. However still, a large number of incurable diseases like cancer, AIDS, Alzheimer’s disease are highly prevalent where rational approaches are attempting to develop newer and newer therapeutic agents. Topological indices used in combination with other molecular descriptors may prove to be highly beneficial in lead discovery. However there is a strong need for further studies with regard to the development of more mathematical models for other diseases as well as for the development of more topostructural/topochemical descriptors with high discriminating power and negligible degeneracy.