Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Graphics and Modelling 26 (2008) 1020–1029
Journal of Molecular Graphics and Modelling
www.elsevier.com/locate/JMGM

# Predicting anti-HIV-1 activity of 6-arylbenzonitriles: Computational approach using superaugmented eccentric connectivity topochemical indices

Harish Dureja [a], Sunil Gupta [b], A.K. Madan [a,*]

[a] Faculty of Pharmaceutical Sciences, M.D. University, Rohtak 124 001, India
[b] Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Quinta da Torre, 2829-516 Caparica, Portugal

Received 9 April 2007; received in revised form 20 August 2007; accepted 25 August 2007
Available online 31 August 2007

**Abstract**

Highly discriminating adjacency-cum-distance based topochemical indices termed as superaugmented eccentric connectivity topochemical indices for quantitative structure–activity and structure–property relationships (QSAR/QSPR) have been conceptualized in the present study. These indices were found to exhibit high sensitivity towards the presence and relative position of heteroatom(s), exceptionally high discriminating power and negligible degeneracy for all possible structures of five vertices containing one heteroatom. Utility of these indices was investigated for development of models for prediction of anti-human immunodeficiency virus (HIV)-1 activity using a data set comprising 81 differently substituted 6-arylbenzonitriles. The values of the superaugmented eccentric connectivity topochemical indices of all the analogues comprising the data set were computed using an in-house computer program. The resultant data was analyzed and suitable models were developed after identification of the active ranges. Subsequently, a biological activity was assigned to each analogue using these models which was then compared with the reported anti-HIV-1 activity. The accuracy of prediction was found to be ~81% for all the three topochemical models. High sensitivity towards presence and relative position of heteroatom(s), exceptionally high discriminating power amalgamated with low degeneracy offer proposed topochemical indices vast potential for isomer discrimination, similarity/dissimilarity, drug design, quantitative structure–activity/structure–property relationships, lead optimization and combinatorial library design.


*Keywords:* Superaugmented eccentric connectivity topochemical index; Topochemical indices; Anti-HIV-1 activity; 6-Arylbenzonitriles; Structure–activity relationship

## 1. Introduction

The most critical step in drug discovery continues to be the identification and optimization of lead compounds in a rapid and cost effective way. The *computer-aided drug discovery* (CADD) approach is complementary to the real world of synthesis and screening. It ''involves all computer-assisted techniques used to discover, design and optimize compounds with desired structure and properties'' [1]. Formulation of quantitative relations among changes in the structural features and physicochemical properties/biological activities is an interesting task of a computational chemist in view of the potential application of the derived relations in the diagnostic and mechanistic interpretation and prediction of properties/activities [2]. Structure–activity relationships (SARs) are such models, which attempt to relate certain structural aspects of molecules to their physicochemical/biological/toxicological properties [3]. The graph-theoretical approach to quantitative structure–property and structure–activity relationships (QSPR/QSAR) is based on mathematical representation of the molecular structure. The molecular descriptors derived therefrom are commonly named topological indices (TIs) [4]. Topological descriptors have gained considerable popularity as these can be derived from molecular structures using low computational resources [2]. TIs have the advantage that, unlike other molecular descriptors, they can be computed

* Corresponding author. Tel.: +91 98963 46211.
*E-mail address:* madan_ak@yahoo.com (A.K. Madan).

1093-3263/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.jmgm.2007.08.008

rapidly for any known or unknown chemical structure [5]. The application of TIs to the design and selection of novel active compounds is probably one of the most active areas of research on the application of such descriptors to biological problems [1]. The use of these descriptors covers most areas of the drug development process: lead discovery and lead optimization. They also include virtual screening, drug design, combinatorial library design, QSPR/QSAR, structure–pharmacokinetics, structure–toxicity relationships, and so forth [6]. The topostructural and topochemical descriptors are collectively referred to as topological descriptors. Topostructural descriptors encode information strictly on the adjacency and connectedness of atoms within a molecule whereas topochemical descriptors encode information relating to both molecular topology and the chemical nature of atoms and bonds within a molecule [7]. These indices are derived from matrices, like distance matrix and/or adjacency matrix, which represent a molecular graph. When the distance or adjacency matrix is weighted corresponding to the heteroatom(s) like N, O, Cl, etc., in a molecule, the matrix may be termed as chemical distance or chemical adjacency matrix, respectively. Indices or descriptors derived from such matrices are known as topochemical indices or topochemical descriptors.

Despite advances made in the therapeutic management, human immunodeficiency virus (HIV) infection has remained an intractable problem, and complete eradication of the virus an unrealized goal [8]. The human immunodeficiency virus is the cause of the acquired immunodeficiency syndrome (AIDS). Various compounds have been reported by De Clercq to inhibit the replication of causative retrovirus called HIV-1, *in vitro* [9]. In 1987, zidovudine (azidothymidine, AZT), a nucleoside RT inhibitor (NRTI), was approved in the USA as the first chemotherapeutic agent against HIV/AIDS [10,11]. A new diarylpyrimidine (DAPY) non-nucleoside reverse transcriptase inhibitor (NNRTI) was found to be suitable for high compliance oral treatment of HIV-1 infection [12]. However, resistance to anti-HIV compounds develops rapidly, sometimes within a few days of initiating treatment [13,14]. Acyclic nucleoside phosphonates (such as cidofovir, adefovir and tenofovir) bring a new dimension to the therapy of viral infections, as they offer a broader spectrum of activity, a longer duration of antiviral action and a lower risk of resistance development compared with available treatments [15]. Successful applications of multi-drug cocktails using inhibitors of HIV-1 protease and reverse transcriptase have been hailed as milestone in the treatment of AIDS [16]. Anti-HIV therapy, today, is in need of new drugs, which are less toxic, active against the drug resistant mutants selected by current therapies, or addressed towards novel targets in the viral replicative cycle [17,18].

In the present study, the relationship between adjacency-cum-distance based topochemical indices termed as superaugmented eccentric connectivity topochemical indices and anti-HIV-1 activity of 6-arylbenzonitriles has been investigated and suitable models developed for prediction of anti-HIV-1 activity.

## 2. Methodology

### 2.1. Calculation of topological indices

Three adjacency-cum-distance based topochemical indices termed as superaugmented eccentric connectivity topochemical indices, i.e. superaugmented eccentric connectivity topochemical index-1 ($^{SAc}\xi_1^c$), superaugmented eccentric connectivity topochemical index-2 ($^{SAc}\xi_2^c$) and superaugmented eccentric connectivity topochemical index-3 ($^{SAc}\xi_3^c$) have been proposed in the present study.

### 2.2. Superaugmented eccentric connectivity topochemical index-1

The superaugmented eccentric connectivity topochemical index-1, denoted by $^{SAc}\xi_1^c$, is defined as the summation of the quotients of the product of adjacent vertex chemical degrees and squared chemical eccentricity of the concerned vertex, for all vertices in the hydrogen suppressed molecular graph.

It is expressed as;

$$^{SAc}\xi_1^c = \sum_{i=1}^{n}\left(\frac{M_{ic}}{E_{ic}^2}\right) \quad (1)$$

where $M_{ic}$ is the product of chemical degrees of all vertices ($v_j$), adjacent to vertex $i$, $E_{ic}$ is the chemical eccentricity, and $n$ is the number of vertices in graph $G$.

### 2.3. Superaugmented eccentric connectivity topochemical index-2

The superaugmented eccentric connectivity topochemical index-2, denoted by $^{SAc}\xi_2^c$, can be defined as the summation of the quotients of the product of adjacent vertex chemical degrees and cubic chemical eccentricity of the concerned vertex, for all vertices in the hydrogen suppressed molecular graph.

It can be expressed as;

$$^{SAc}\xi_2^c = \sum_{i=1}^{n}\left(\frac{M_{ic}}{E_{ic}^3}\right) \quad (2)$$

where $M_{ic}$ is the product of chemical degrees of all vertices ($v_j$), adjacent to vertex $i$, $E_{ic}$ is the chemical eccentricity, and $n$ is the number of vertices in graph $G$.

### 2.4. Superaugmented eccentric connectivity topochemical index-3

The superaugmented eccentric connectivity topochemical index-3, denoted by $^{SAc}\xi_3^c$, is defined as the summation of the quotients of the product of adjacent vertex chemical degrees and fourth power of chemical eccentricity of the concerned vertex, for all vertices in the hydrogen suppressed molecular

graph. It is expressed as;

$$^{SAc}\xi_3^c = \sum_{i=1}^{n}\left(\frac{M_{ic}}{E_{ic}^4}\right) \quad (3)$$

where $M_{ic}$ is the product of chemical degrees of all vertices ($v_j$), adjacent to vertex $i$, $E_{ic}$ is the chemical eccentricity, and $n$ is the number of vertices in graph $G$.

Superaugmented eccentric connectivity topochemical indices can be easily calculated from the chemical distance matrix ($D_c$) and augmentative chemical adjacency matrix ($A_c^\alpha$) obtained by modifying chemical adjacency matrix ($A_c$). The derivation of matrices for calculation of superaugmented eccentric connectivity topochemical index-1 ($^{SAc}\xi_1^c$), superaugmented eccentric connectivity topochemical index-2 ($^{SAc}\xi_2^c$) and superaugmented eccentric connectivity topochemical index-3 ($^{SAc}\xi_3^c$) for three isomers of eight membered molecule (heptylamine) has been exemplified in Fig. 1. The sensitivity of the proposed topochemical descriptors towards presence and relative position of heteroatom(s) for all three, four and five membered isomers containing one heteroatom has been illustrated in Table 1. Discriminating power and degeneracy of the superaugmented eccentric connectivity topochemical indices were investigated using all possible structures with three, four and five vertices containing one heteroatom (Table 2).

### 2.5. Model development

A data set [19] comprising 81 analogues of 6-arylbenzonitriles was selected for the present investigation. The basic structure for these analogues is depicted in Fig. 2 and various substituents are enlisted in Table 3.

The values of all the three superaugmented eccentric connectivity topochemical indices were computed for each analogue using an in-house computer program based on the method explained in Fig. 1. For the selection and evaluation of range specific features, exclusive activity ranges were determined from the frequency distribution of response level and subsequently identifying the active range by analyzing the resultant data by maximization of the moving average with respect to the active compounds (<35% = inactive, 35–65% = transitional, >65% = active) [20]. Subsequently, each analogue was assigned a biological activity, which was then compared with the reported [19] anti-HIV-1 activity. The anti-HIV-1 activity was reported quantitatively as $IC_{50}$ (μM) values in different concentrations. The analogues possessing $IC_{50}$ values of ≤1.0 μM were considered to be active and analogues possessing $IC_{50}$ values of >1.0 μM were considered to be inactive for the purpose of present study. The percentage degree of prediction of a particular range and overall degree of prediction of each model were also determined. The results are summarized in Tables 1–4 and Figs. 1–3.

## 3. Results and discussion

The main hypothesis in the QSPR and QSAR approach is that information about all properties (physical, chemical, and biological) of a chemical substance can be derived from its molecular structure. An inspection of the published QSPR and QSAR models shows that molecular graph descriptors/TIs are used with success in modeling various properties and demonstrates that they are valuable descriptors of chemical structure [21]. In recent years, TIs have been reported and utilized for chemical documentation, isomer discrimination, study of molecular complexity, chirality, similarity/dissimilarity, QSAR/QSPR, drug design and database selection, lead optimization, rational combinatorial library design and for deriving multilinear regression models [1,22]. High discriminating power and absence of degeneracy are two properties of an ideal topological index, which the researchers in theoretical chemistry are striving to achieve.

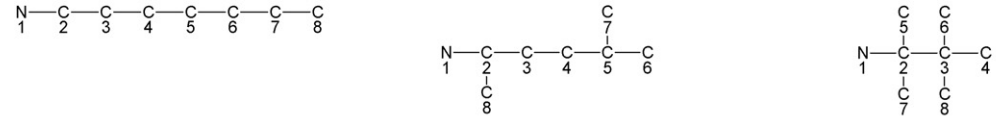
In the present study, three novel superaugmented eccentric connectivity topochemical indices, denoted by $^{SAc}\xi^c$ have been conceptualized. These indices can be easily calculated from chemical distance matrix ($D_c$) and augmentative chemical adjacency matrix ($A_c^\alpha$). The consideration of both eccentricity and degree of the vertices results in significant changes in the topochemical indices value with a minor change in the branching of molecules.

As observed from Fig. 1, the value of superaugmented eccentric connectivity topochemical index-1 changes by about five times (from 0.995 to 4.473), the value of superaugmented eccentric connectivity topochemical index-2 changes by more than eight times (from 0.211 to 1.750) and the value of superaugmented eccentric connectivity topochemical index-3 changes by more than 16 times (from 0.046 to 0.713) following branching of eight membered molecule. These superaugmented eccentric connectivity topochemical indices were found to be more sensitive towards branching using three isomers of eight membered molecule (heptylamine).

First-generation topological indexes were integer numbers obtained by simple (''bookkeeping'') operations from local vertex invariants, which were integer numbers, involving only one vertex at a time; second-generation TI's were real numbers obtained via sophisticated (''structural'') operations from integer local vertex invariants, involving more than one vertex at a time whereas third-generation TI's are real numbers based on real-number local vertex invariants, having extremely low or no degeneracy [23]. The successful application of topological descriptors is somewhat limited owing to discriminating power of less than two digits only. The highest discriminating power was reported to be 295.4 in respect of augmented eccentric connectivity index [24] for all possible structures containing five vertices. Authors suggest that the topological indices having discriminating power ≥100 for structures containing only five vertices {with or without heteroatom(s)} may be treated as fourth-generation topological descriptors.

The values of superaugmented eccentric connectivity topochemical indices were computed for all the possible structure of three, four and five vertices using in-house computer program. The values and the structures have been presented in Table 1 and their comparison is presented in Table 2. Superaugmented eccentric connectivity topochemical indices have revealed exceptionally high discriminating power.

**Arbitrary vertex numbering**



**Chemical Distance Matrices ($D_c$)**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $E_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | **7** |
| **2** | 1.167 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | **6** |
| **3** | 2.167 | 1 | 0 | 1 | 2 | 3 | 4 | 5 | **5** |
| **4** | 3.167 | 2 | 1 | 0 | 1 | 2 | 3 | 4 | **4** |
| **5** | 4.167 | 3 | 2 | 1 | 0 | 1 | 2 | 3 | **4.167** |
| **6** | 5.167 | 4 | 3 | 2 | 1 | 0 | 1 | 2 | **5.167** |
| **7** | 6.167 | 5 | 4 | 3 | 2 | 1 | 0 | 1 | **6.167** |
| **8** | 7.167 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | **7.167** |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $E_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 1 | 2 | 3 | 4 | 5 | 5 | 2 | **5** |
| **2** | 1.167 | 0 | 1 | 2 | 3 | 4 | 4 | 1 | **4** |
| **3** | 2.167 | 1 | 0 | 1 | 2 | 3 | 3 | 2 | **3** |
| **4** | 3.167 | 2 | 1 | 0 | 1 | 2 | 2 | 3 | **3.167** |
| **5** | 4.167 | 3 | 2 | 1 | 0 | 1 | 1 | 4 | **4.167** |
| **6** | 5.167 | 4 | 3 | 2 | 1 | 0 | 2 | 5 | **5.167** |
| **7** | 5.167 | 4 | 3 | 2 | 1 | 2 | 0 | 5 | **5.167** |
| **8** | 2.167 | 1 | 2 | 3 | 4 | 5 | 5 | 0 | **5** |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $E_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 1 | 2 | 3 | 2 | 3 | 2 | 3 | **3** |
| **2** | 1.167 | 0 | 1 | 2 | 1 | 2 | 1 | 2 | **2** |
| **3** | 2.167 | 1 | 0 | 1 | 2 | 1 | 2 | 1 | **2.167** |
| **4** | 3.167 | 2 | 1 | 0 | 3 | 2 | 3 | 2 | **3.167** |
| **5** | 2.167 | 1 | 2 | 3 | 0 | 3 | 2 | 3 | **3** |
| **6** | 3.167 | 2 | 1 | 2 | 3 | 0 | 3 | 2 | **3.167** |
| **7** | 2.167 | 1 | 2 | 3 | 2 | 3 | 0 | 3 | **3** |
| **8** | 3.167 | 2 | 1 | 2 | 3 | 2 | 3 | 0 | **3.167** |

**Chemical Adjacency Matrices ($A_c$)**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $V_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| **2** | 1.167 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **2.167** |
| **3** | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | **2** |
| **4** | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | **2** |
| **5** | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | **2** |
| **6** | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | **2** |
| **7** | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | **2** |
| **8** | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | **1** |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $V_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| **2** | 1.167 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | **3.167** |
| **3** | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | **2** |
| **4** | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | **2** |
| **5** | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | **3** |
| **6** | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | **1** |
| **7** | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | **1** |
| **8** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $V_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| **2** | 1.167 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | **4.167** |
| **3** | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | **4** |
| **4** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **1** |
| **5** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| **6** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **1** |
| **7** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| **8** | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **1** |

**Augmentative Chemical Adjacency Matrices ($A_c$ )**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $M_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 2.167 | 0 | 0 | 0 | 0 | 0 | 0 | **2.167** |
| **2** | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | **2** |
| **3** | 0 | 2.167 | 0 | 2 | 0 | 0 | 0 | 0 | **4.334** |
| **4** | 0 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | **4** |
| **5** | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 0 | **4** |
| **6** | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | **4** |
| **7** | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | **2** |
| **8** | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | **2** |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $M_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 3.167 | 0 | 0 | 0 | 0 | 0 | 0 | **3.167** |
| **2** | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | **2** |
| **3** | 0 | 3.167 | 0 | 2 | 0 | 0 | 0 | 0 | **6.334** |
| **4** | 0 | 0 | 2 | 0 | 3 | 0 | 0 | 0 | **6** |
| **5** | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 0 | **2** |
| **6** | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | **3** |
| **7** | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | **3** |
| **8** | 0 | 3.167 | 0 | 0 | 0 | 0 | 0 | 0 | **3.167** |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | $M_{ic}$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 4.167 | 0 | 0 | 0 | 0 | 0 | 0 | **4.167** |
| **2** | 1 | 0 | 4 | 0 | 1 | 0 | 1 | 0 | **4** |
| **3** | 0 | 4.167 | 0 | 1 | 0 | 1 | 0 | 1 | **4.167** |
| **4** | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | **4** |
| **5** | 0 | 4.167 | 0 | 0 | 0 | 0 | 0 | 0 | **4.167** |
| **6** | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | **4** |
| **7** | 0 | 4.167 | 0 | 0 | 0 | 0 | 0 | 0 | **4.167** |
| **8** | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | **4** |

**Superaugmented Eccentric Connectivity Topochemical Index -1**

$$^{SAc}\xi^{c}{}_{1} = \sum_{i=1}^{n}\left(\frac{M_{ic}}{E_{ic}{}^{2}}\right)$$

= [2.167/49+2/36+4.334/25+4/16+4/17.4+4/26.7 +2/38+2/51]
= 0.995

= [3.167/25+2/16+6.334/9+6/10.03+2/17.4 +3/26.7+3/26.7+3.167/25]
= 2.020

= [4.167/9+4/4+4.167/4.7+4/10.03+4.167/9+4/10. 03+4.167/9+4/10.03]
= 4.473

**Superaugmented Eccentric Connectivity Topochemical Index -2**

$$^{SAc}\xi^{c}{}_{2} = \sum_{i=1}^{n}\left(\frac{M_{ic}}{E_{ic}{}^{3}}\right)$$

= [2.167/343+2/216+4.334/125+4/64+4/72.4+4/ 137.9+2/234.5+2/368.1]
= 0.211

= [3.167/125+2/64+6.334/27+6/31.8+2/72. 4+3/137.9+3/137.9+3.167/125]
= 0.577

= [4.167/27+4/8+4.167/10.2+4/31.8+4.167/27+4/ 31.8+4.167/27+4/31.8]
= 1.750

**Superaugmented Eccentric Connectivity Topochemical Index - 3**

$$^{SAc}\xi^{c}{}_{3} = \sum_{i=1}^{n}\left(\frac{M_{ic}}{E_{ic}{}^{4}}\right)$$

= [2.167/2401+2/1296+4.334/625+4/256+4/301. 5+4/712.8+2/1446.4+2/2638.5]
= 0.046

= [3.167/625+2/256+6.334/81+6/100.6+2/3 01.5+3/712.8+3/712.8+3.167/625]
= 0.171

= [4.167/81+4/16+4.167/22.1+4/100.6+4.167/81+ 4/100.6+4.167/81+4/100.6]
= 0.713

Fig. 1. Calculation of values of superaugmented eccentric connectivity topochemical index-1 ($^{SAc}\xi_1^c$), superaugmented eccentric connectivity topochemical index-2 ($^{SAc}\xi_2^c$) and superaugmented eccentric connectivity topochemical index-3 ($^{SAc}\xi_3^c$) for three isomers of eight membered molecule (heptylamine).

Table 1
Index values of for all possible structure with three, four and five vertices containing one heteroatom

| Compound number | Structure | $^{SAc}\xi_1^c$ | $^{SAc}\xi_2^c$ | $^{SAc}\xi_3^c$ |
|---|---|---|---|---|
| 1 |  | 2.214 | 1.755 | 1.543 |
| 2 |  | 1.737 | 1.113 | 0.773 |
| 3 |  | 12.123 | 11.061 | 10.150 |
| 4 |  | 1.402 | 0.606 | 0.270 |
| 5 |  | 1.474 | 0.644 | 0.290 |
| 6 |  | 2.875 | 1.648 | 1.024 |
| 7 |  | 3.506 | 2.474 | 1.997 |
| 8 |  | 4.174 | 2.048 | 1.006 |
| 9 |  | 8.888 | 7.053 | 6.206 |
| 10 |  | 7.156 | 4.688 | 3.305 |
| 11 |  | 6.427 | 4.158 | 2.929 |
| 12 |  | 29.967 | 26.111 | 23.655 |
| 13 |  | 23.247 | 18.181 | 14.742 |
| 14 |  | 98.047 | 88.562 | 80.434 |
| 15 |  | 2.078 | 0.859 | 0.367 |
| 16 |  | 2.050 | 0.857 | 0.372 |
| 17 |  | 2.181 | 0.921 | 0.405 |
| 18 |  | 2.191 | 0.921 | 0.402 |
| 19 |  | 1.595 | 0.624 | 0.256 |
| 20 |  | 1.579 | 0.610 | 0.247 |
| 21 |  | 1.822 | 0.773 | 0.348 |
| 22 |  | 4.438 | 2.379 | 1.366 |
| 23 |  | 20.620 | 14.716 | 11.188 |
| 24 |  | 4.723 | 2.225 | 1.049 |
| 25 |  | 20.466 | 13.410 | 9.484 |
| 26 |  | 22.374 | 14.845 | 10.570 |
| 27 |  | 18.727 | 12.166 | 8.620 |
| 28 |  | 4.974 | 2.298 | 1.079 |

Table 1 (*Continued*)

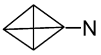
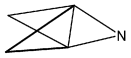
| Compound number | Structure | $^{SAc}\xi_1^c$ | $^{SAc}\xi_2^c$ | $^{SAc}\xi_3^c$ |
|---|---|---|---|---|
| 29 |  | 4.821 | 2.230 | 1.051 |
| 30 |  | 4.448 | 1.988 | 0.903 |
| 31 |  | 4.693 | 2.107 | 0.963 |
| 32 |  | 11.461 | 5.647 | 2.785 |
| 33 |  | 10.779 | 5.225 | 2.537 |
| 34 |  | 45.738 | 32.509 | 24.641 |
| 35 |  | 49.571 | 35.468 | 26.931 |
| 36 |  | 44.826 | 28.566 | 19.920 |
| 37 |  | 53.225 | 34.464 | 23.973 |
| 38 |  | 12.318 | 5.608 | 2.585 |
| 39 |  | 146.750 | 114.733 | 92.863 |
| 40 |  | 136.677 | 106.796 | 86.690 |
| 41 |  | 104.383 | 75.504 | 57.865 |
| 42 |  | 377.743 | 311.139 | 260.574 |
| 43 |  | 5.523 | 2.518 | 1.162 |
| 44 |  | 6.378 | 3.072 | 1.497 |
| 45 |  | 6.025 | 2.768 | 1.288 |
| 46 |  | 4.090 | 1.710 | 0.740 |
| 47 |  | 4.033 | 1.685 | 0.727 |
| 48 |  | 4.695 | 2.044 | 0.923 |
| 49 |  | 4.507 | 1.946 | 0.868 |
| 50 |  | 13.050 | 6.202 | 2.984 |
| 51 |  | 11.592 | 5.260 | 2.414 |
| 52 |  | 14.364 | 6.947 | 3.395 |
| 53 |  | 24.323 | 11.668 | 5.606 |

Table 1 (*Continued*)

| Compound number | Structure | $^{SAc}\xi_1^c$ | $^{SAc}\xi_2^c$ | $^{SAc}\xi_3^c$ |
|---|---|---|---|---|
| 54 |  | 26.654 | 13.103 | 6.469 |
| 55 |  | 27.100 | 13.468 | 6.696 |
| 56 |  | 8.416 | 5.085 | 3.362 |
| 57 |  | 9.298 | 5.716 | 3.800 |
| 58 |  | 11.731 | 5.682 | 2.759 |
| 59 |  | 11.162 | 5.390 | 2.607 |
| 60 |  | 11.539 | 5.666 | 2.785 |
| 61 |  | 60.692 | 47.533 | 38.607 |

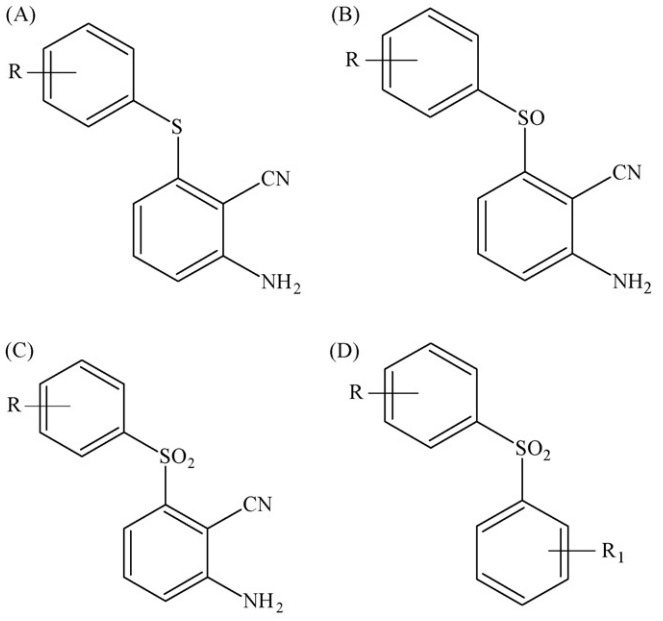



Fig. 2. Basic structures of 6-arylbenzonitriles.

The discriminating power may be defined as the ratio of highest to lowest value for all possible structures of same number of vertices. The ratio of highest to lowest value for all possible structure of five vertices containing a heteroatom in case of superaugmented eccentric connectivity topochemical index-1 is 239, superaugmented eccentric connectivity topochemical index-2 is 510 and superaugmented eccentric connectivity topochemical index-3 is 1055, respectively. Exceptionally high discriminating power of the proposed new generation indices makes it more sensitive towards any change in molecular structure. Extreme sensitivity towards branching as well as discriminating power of all the three proposed indices is clearly evident from the respective index values of all the possible structures with five vertices containing one heteroatom (Table 1).

Table 2
Comparison of discriminating power and degeneracy of superaugmented eccentric connectivity topochemical indices using all possible structures having three, four and five vertices containing one heteroaom

| | $^{SAc}\xi_1^c$ | $^{SAc}\xi_2^c$ | $^{SAc}\xi_3^c$ |
|---|---|---|---|
| For three vertices | | | |
| Minimum value | 1.737 | 1.113 | 0.773 |
| Maximum value | 11.061 | 10.150 | 9.369 |
| Ratio | 1:6.368 | 1:9.119 | 1:12.12 |
| Degeneracy[a] | 0/3 | 0/3 | 0/3 |
| For four vertices | | | |
| Minimum value | 1.402 | 0.610 | 0.270 |
| Maximum value | 98.047 | 88.562 | 80.434 |
| Ratio | 1:70 | 1:146 | 1:298 |
| Degeneracy | | 0/11 | 0/11 |
| For five vertices | | | |
| Minimum value | 1.579 | 0.610 | 0.247 |
| Maximum value | 377.743 | 311.139 | 260.574 |
| Ratio | 1:239 | 1:510 | 1:1055 |
| Degeneracy | 0/47 | 1/47 | 1/47 |

[a] Degeneracy = Number of compounds having same values/total number of compounds with same number of vertices.

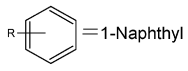
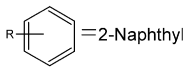
Degeneracy is the measure of ability of an index to differentiate between the relative positions of atom in a molecule. The superaugmented eccentric connectivity topochemical index-1 did not exhibit any degeneracy for all possible structures with three, four and five vertices with a heteroatom, whereas the superaugmented eccentric connectivity index-2 and superaugmented eccentric connectivity topochemical index-3 has very low degeneracy of one in case of all possible structures with five vertices containing one heteroatom (Table 2). Extremely low degeneracy indicates the enhanced capability of these indices to differentiate and demonstrate slight variations in the molecular structure. This means that the likeliness of different structures to have same value is extremely remote.

Relationship of superaugmented eccentric connectivity topochemical indices with anti-HIV-1 activity of 6-arylbenzonitriles was studied and suitable models were developed for prediction of anti-HIV-1 activity. Though all the analogues in the datasets possess varying degree of biological activity but only those analogues having $IC_{50}$ values of $\leq 1.0$ μM were considered to be active for the purpose of present study. The methodology used in the present studies aims at the development of suitable models for providing lead molecules through exploitation of the active ranges in the proposed models based on topochemical indices. Proposed models are unique and differ widely from conventional QSAR models. Both system of modeling have their advantages and limitations. In the modeling used in this study, the system adopted has distinct advantage of identification of narrow active ranges, which may be erroneously skipped during routine regression analysis in conventional QSAR. Since the ultimate goal of modeling is to provide lead structures, therefore, active range(s) of the proposed model(s) can play vital role in providing lead structures [25].

Table 3
Relationship of superaugmented eccentric connectivity topochemical indices with anti-HIV-1 activity of 6-arylbenzonitriles

| Compound number | $R$ | $R_1$ | $^{SAc}\xi_1^c$ | $^{SAc}\xi_2^c$ | $^{SAc}\xi_3^c$ | Anti-HIV-1 activity predicted reported | | | | Reported $IC_{50}$ (μM) values [19] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $^{SAc}\xi_1^c$ | $^{SAc}\xi_2^c$ | $^{SAc}\xi_3^c$ | Reported | |
| $A_1$ | H | – | 3.145 | 0.546 | 0.104 | – | – | – | – | 14.6 |
| $A_2$ | 2-$OCH_3$ | – | 3.325 | 0.541 | 0.097 | – | – | – | – | 4.3 |
| $A_3$ | 3-$OCH_3$ | – | 2.552 | 0.353 | 0.052 | – | – | – | – | 6.0 |
| $A_4$ | 4-$OCH_3$ | – | 2.074 | 0.256 | 0.033 | – | – | – | – | 16.0 |
| $A_5$ | 2-$CH_3$ | – | 3.295 | 0.566 | 0.107 | – | – | – | – | 6.1 |
| $A_6$ | 3-$CH_3$ | – | 3.273 | 0.561 | 0.106 | – | – | – | – | 115 |
| $A_7$ | 4-$CH_3$ | – | 2.564 | 0.376 | 0.059 | – | – | – | – | 4.1 |
| $A_8$ | 2-Cl | – | 2.904 | 0.427 | 0.067 | – | – | – | – | 7.4 |
| $A_9$ | 3-Cl | – | 2.38 | 0.306 | 0.041 | – | – | – | – | 32.0 |
| $A_{10}$ | 4-Cl | – | 1.928 | 0.227 | 0.028 | – | – | – | – | 30.0 |
| $A_{11}$ | 2-Br | – | 2.069 | 0.23 | 0.026 | – | – | – | – | 5.1 |
| $A_{12}$ | 3-Br | – | 1.894 | 0.201 | 0.022 | – | – | – | – | 9.8 |
| $A_{13}$ | 3-F | – | 2.946 | 0.461 | 0.079 | – | – | – | – | 6.4 |
| $A_{14}$ | 2-CN | – | 3.441 | 0.58 | 0.108 | – | – | – | – | 1.73 |
| $A_{15}$ | 3-CN | – | 2.601 | 0.369 | 0.056 | – | – | – | – | 43.8 |
| $A_{16}$ | 4-CN | – | 2.108 | 0.265 | 0.035 | – | – | – | – | 12.8 |
| $A_{17}$ | 3-$CF_3$ | – | 2.712 | 0.355 | 0.049 | – | – | – | – | 31.5 |
| $A_{18}$ | 5-$NH_2$ | – | 3.238 | 0.553 | 0.105 | | | | + | >0.8 |
| $A_{19}$ | 2,5-$Cl_2$ | – | 2.772 | 0.359 | 0.048 | – | – | – | + | 0.43 |
| $A_{20}$ | 3,5-$(CH_3)_2$ | – | 3.411 | 0.577 | 0.108 | – | – | – | – | 62%@5 μM |
| $A_{21}$ | 3,5-$Cl_2$ | – | 2.807 | 0.356 | 0.047 | – | – | – | – | 1.76 |
| $A_{22}$ | 3-Cl, 5-$CH_3$ | – | 2.538 | 0.324 | 0.043 | – | – | – | – | 2.0 |
| $A_{23}$ | 3-$OCH_3$, 5-$CH_3$ | – | 2.693 | 0.369 | 0.054 | – | – | – | – | 5.1 |
| $A_{24}$ | 3-$OCH_3$, 5-$CF_3$ | – | 2.968 | 0.384 | 0.052 | – | – | – | – | 93.5 |
| $B_1$ | 2-$OCH_3$ | – | 5.68 | 1.048 | 0.208 | – | + | ± | – | 4.8 |
| $B_2$ | 3-$OCH_3$ | – | 4.12 | 0.631 | 0.102 | – | – | – | – | 16.0 |
| $B_3$ | 4-$OCH_3$ | – | 3.233 | 0.432 | 0.06 | – | – | – | – | >200 |
| $B_4$ | 2-$CH_3$ | – | 5.809 | 1.13 | 0.237 | – | ± | – | – | 93.0 |
| $B_5$ | 3-$CH_3$ | – | 5.73 | 1.117 | 0.235 | – | ± | ± | – | 29.23 |
| $B_6$ | 4-$CH_3$ | – | 4.323 | 0.709 | 0.123 | – | – | – | – | 49.0 |
| $B_7$ | 2-Br | – | 3.033 | 0.345 | 0.04 | – | – | – | – | 39.2 |
| $B_8$ | 3-Br | – | 2.428 | 0.256 | 0.028 | – | – | – | + | 0.08 |
| $B_9$ | 4-Br | – | 1.893 | 0.183 | 0.018 | – | – | – | – | 20.21 |
| $B_{10}$ | 2-CN | – | 5.946 | 1.143 | 0.238 | – | ± | – | – | 3.9 |
| $B_{11}$ | 3-CN | – | 4.259 | 0.672 | 0.112 | – | – | – | – | 14.2 |
| $B_{12}$ | 4-CN | – | 3.322 | 0.453 | 0.064 | – | – | – | – | >200 |
| $B_{13}$ | 3-$CF_3$ | – | 4.157 | 0.6 | 0.091 | – | – | – | – | 40.0 |
| $B_{14}$ | 3,5-$(CH_3)_2$ | – | 5.868 | 1.133 | 0.236 | – | ± | ± | + | 0.34 |
| $B_{15}$ | 2,5-$Cl_2$ | – | 4.23 | 0.59 | 0.085 | – | – | – | – | 9.85 |
| $B_{16}$ | 3-Cl, 5-$CH_3$ | – | 3.827 | 0.53 | 0.077 | – | – | – | + | 0.32 |
| $B_{17}$ | 3-$OCH_3$, 5-$CF_3$ | – | 4.413 | 0.629 | 0.095 | – | – | – | – | 2.07 |
| $C_1$ | H | – | 11.601 | 2.503 | 0.563 | – | – | – | – | 2.0 |
| $C_2$ | 2-$OCH_3$ | – | 11.314 | 2.307 | 0.493 | – | – | – | + | 0.6 |
| $C_3$ | 3-$OCH_3$ | – | 7.857 | 1.314 | 0.227 | + | ± | ± | + | 0.9 |
| $C_4$ | 4-$OCH_3$ | – | 5.934 | 0.849 | 0.125 | – | – | – | – | 25 |
| $C_5$ | 2-$CH_3$ | – | 11.865 | 2.539 | 0.568 | – | – | – | – | 2.3 |
| $C_6$ | 3-$CH_3$ | – | 11.729 | 2.518 | 0.565 | – | – | – | + | 0.4 |
| $C_7$ | 4-$CH_3$ | – | 8.549 | 1.531 | 0.285 | – | – | – | – | 9.5 |
| $C_8$ | 2-Cl | – | 9.322 | 1.66 | 0.307 | – | – | – | – | 4.1 |
| $C_9$ | 3-Cl | – | 6.699 | 1.009 | 0.156 | + | + | + | + | 0.59 |
| $C_{10}$ | 4-Cl | – | 5.18 | 0.685 | 0.092 | – | – | – | – | 3.0 |
| $C_{11}$ | 2-Br | – | 4.824 | 0.555 | 0.065 | – | – | – | – | 5.0 |
| $C_{12}$ | 3-Br | – | 3.628 | 0.379 | 0.04 | – | – | – | + | 0.54 |
| $C_{13}$ | 4-Br | – | 2.88 | 0.274 | 0.027 | – | – | – | – | 20.0 |
| $C_{14}$ | 2-F | – | 12.004 | 2.559 | 0.571 | – | – | – | – | 3.0 |
| $C_{15}$ | 3-F | – | 9.995 | 1.944 | 0.394 | – | – | – | – | 3.0 |
| $C_{16}$ | 2-CN | – | 11.994 | 2.55 | 0.569 | – | – | – | – | 5.4 |
| $C_{17}$ | 3-CN | – | 8.229 | 1.42 | 0.254 | – | – | – | – | 2.4 |
| $C_{18}$ | 4-CN | – | 6.162 | 0.903 | 0.136 | – | + | + | – | 80.0 |
| $C_{19}$ | 3-$CF_3$ | – | 7.584 | 1.198 | 0.196 | + | ± | ± | – | 3.5 |
| $C_{20}$ | 2,5-$Cl_2$ | – | 7.43 | 1.111 | 0.171 | + | + | + | + | 0.3 |
| $C_{21}$ | 3,5-$Cl_2$ | – | 7.127 | 1.058 | 0.162 | + | + | + | + | 0.07 |

Table 3 (*Continued*)

| Compound number | *R* | $R_1$ | $^{SAc}\xi_1^c$ | $^{SAc}\xi_2^c$ | $^{SAc}\xi_3^c$ | Anti-HIV-1 activity predicted reported | | | | Reported $IC_{50}$ (μM) values [19] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $^{SAc}\xi_1^c$ | $^{SAc}\xi_2^c$ | $^{SAc}\xi_3^c$ | Reported | |
| $C_{22}$ | 3,5-$(CH_3)_2$ | – | 11.867 | 2.534 | 0.567 | – | – | – | + | 0.01 |
| $C_{23}$ | 3-Br, 5-$CH_3$ | – | 3.798 | 0.396 | 0.042 | – | – | – | + | 0.02 |
| $C_{24}$ | 3-Cl, 5-$CH_3$ | – | 6.858 | 1.027 | 0.158 | + | + | + | + | 0.03 |
| $C_{25}$ | 3-$OCH_3$, 5-$CH_3$ | – | 7.999 | 1.33 | 0.229 | + | ± | ± | + | 0.05 |
| $C_{26}$ | 3-$OCH_3$, 5-$CF_3$ | – | 7.84 | 1.228 | 0.2 | + | ± | ± | + | 0.09 |
| $C_{27}$ | 3-OH, 5-$CH_3$ | – | 11.09 | 2.272 | 0.488 | – | – | – | + | 0.43 |
| $C_{28}$ | 3-$OCH_2CH_3$, 5-$CH_3$ | – | 6.207 | 0.881 | 0.128 | + | + | + | + | 0.06 |
| $C_{29}$ | 3-$O(CH_2)_2CH_3$, 5-$CH_3$ | – | 5.065 | 0.638 | 0.082 | – | – | – | + | 0.06 |
| $C_{30}$ | 3-$O(CH_2)_3CH_3$, 5-$CH_3$ | – | 4.219 | 0.48 | 0.056 | – | – | – | + | 0.6 |
| $C_{31}$ |  =1-Naphthyl | – | 9.314 | 1.627 | 0.297 | – | – | – | – | 3.32 |
| $C_{32}$ |  =2-Naphthyl | – | 6.753 | 1.001 | 0.153 | + | + | + | + | 0.05 |
| $D_1$ | 2-$NO_2$ | – | 10.329 | 2.056 | 0.426 | – | – | – | – | 8.6 |
| $D_2$ | 2-$NO_2$ | 2-$NO_2$ | 10.852 | 2.105 | 0.43 | – | – | – | – | 2.2 |
| $D_3$ | 3,5-$Cl_2$ | 2-CN, 3-F | 7.026 | 1.034 | 0.158 | + | + | + | – | 42 |
| $D_4$ | 3,5-$(CH_3)_2$ | 2-CN, 3-F | 10.273 | 1.987 | 0.401 | – | – | – | – | 1.5 |
| $D_5$ | 3-$OCH_3$, 5-$CH_3$ | 2-CN, 3-F | 7.94 | 1.314 | 0.226 | + | ± | ± | – | 51 |
| $D_6$ | 3,5-$(CH_3)_2$ | 2-CN, 3-NH-$(CH2)_3CH_3$ | 4.623 | 0.551 | 0.067 | – | – | – | – | >12 |
| $D_7$ | 3,5-$(CH_3)_2$ | 2-CN, 3-cyclo-hexylamnio | 4.797 | 0.566 | 0.068 | – | – | – | – | >200 |
| $D_8$ | H | 3-$NH_2$ | 11.008 | 2.423 | 0.552 | – | – | – | – | >50 |

(+) Active analogue; (−) inactive analogue; (±) analogue in the transitional range where activity could not be specifically assigned.

Retrofit analysis of the data in Tables 3 and 4 reveals the following information with regard to models based upon superaugmented eccentric connectivity topochemical index-1:

- All the compounds were classified either as active or inactive using the model based upon superaugmented eccentric connectivity topochemical index-1. The overall accuracy of prediction was found to be 80% with regard to anti-HIV-1 activity.
- The active range had superaugmented eccentric connectivity topochemical index-1 values of 6.207–7.999. Seventy five percent of the analogues in the active range exhibited anti-HIV-1. The average $IC_{50}$ value of correctly predicted compounds in the active range was found to be only 0.238 μM. This clearly indicates exceptionally high potency of the active range.
- Two inactive ranges—a lower inactive range with index values of <6.207 and an upper inactive range with index values of >7.999 were observed. Activity of 56 out of 69 compounds in these inactive ranges was predicted correctly.
- The ratio of average $IC_{50}$ values of active range and lower inactive range for correctly predicted analogues was found to be 1:158.79 and ratio of average $IC_{50}$ values of active range and upper inactive range for correctly predicted analogues was found to be 1:31.45.

Retrofit analysis of the data in Tables 3 and 4 reveals the following information with regard to model based

Table 4
Proposed models for the prediction of anti-HIV-1 activity of 6-arylbenzonitriles

| Index | Nature of range in the proposed model | Index value | Number of analogues in the range | Number of analogues predicted correctly | Percent accuracy | Overall accuracy of prediction | Average $IC_{50}$ (mM) of correctly predicted analogues |
|---|---|---|---|---|---|---|---|
| $^{SAc}\xi_1^c$ | Lower inactive | <6.207 | 52 | 43 | 82.69 | 80.25 | 37.792 |
| | Active | 6.207–7.999 | 12 | 9 | 75 | | 0.238 |
| | Upper inactive | >7.999 | 17 | 13 | 76.47 | | 7.486 |
| $^{SAc}\xi_2^c$ | Lower inactive | <0.881 | 46 | 38 | 82.61 | 80.56 | 37.214 |
| | Active | 0.881–1.111 | 9 | 6 | 66.67 | | 0.183 |
| | Transitional | >1.111 to <1.42 | 9 | N.A. | N.A. | | N.A. |
| | Upper inactive | >1.42 | 17 | 14 | 82.35 | | 6.951 |
| $^{SAc}\xi_3^c$ | Lower inactive | <0.128 | 46 | 38 | 82.61 | 80.82 | 37.214 |
| | Active | 0.128–0.171 | 8 | 6 | 75 | | 0.183 |
| | Transitional | >0.171 to <0.237 | 8 | N.A. | N.A. | | N.A. |
| | Upper inactive | >0.237 | 19 | 15 | 78.95 | | 12.948 |

N.A., not applicable.

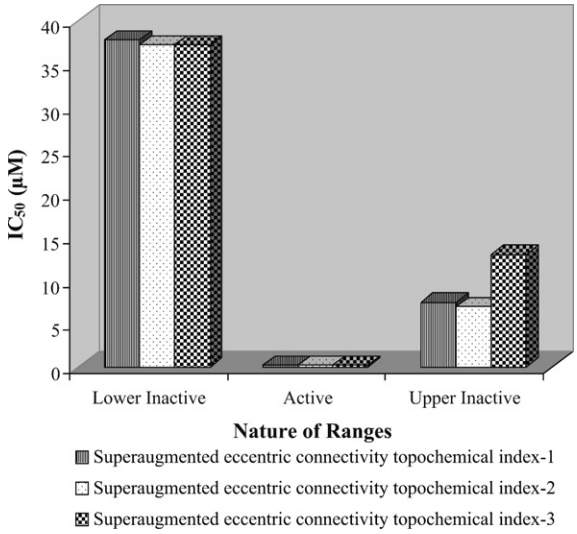



Fig. 3. Average $IC_{50}$ (μM) values of 6-arylbenzonitriles of correctly predicted analogues in various ranges of topochemical models.

upon superaugmented eccentric connectivity topochemical index-2:

- A total of 72 out of 81 compounds were classified either as active or inactive using model based upon superaugmented eccentric connectivity topochemical index-2. The overall accuracy of prediction was found to be ∼81% with regard to anti-HIV-1 activity.
- The active range had superaugmented eccentric connectivity topochemical index-2 values of 0.881–1.111. Approximately sixty seven percent of the analogues in the active range exhibited anti-HIV-1 activity. The average $IC_{50}$ value of correctly predicted compounds in the active range was found to be only 0.183 μM. This clearly indicates exceptionally high potency of the active range.
- Two inactive ranges—a lower inactive range with index values of $<0.881$ and an upper inactive range with index values of $>1.42$ were observed. Activity of 52 out of 63 compounds in these inactive ranges was predicted correctly.
- A transitional range with index values of $>1.111$ to $<1.42$ was observed. The transitional range indicates gradual transition from active to inactive range and vice versa.
- The ratio of average $IC_{50}$ values of active range and lower inactive range for correctly predicted analogues was found to be 1:203.36 and ratio of average $IC_{50}$ values of active range and upper inactive range for correctly predicted analogues was found to be 1:37.98.

Retrofit analysis of the data in Tables 3 and 4 reveals the following information with regard to superaugmented eccentric connectivity topochemical index-3:

- A total of 73 out of 81 compounds were classified either as active or inactive using model based upon superaugmented eccentric connectivity topochemical index-3. The overall accuracy of prediction was found to be ∼81% with regard to anti-HIV activity.
- The active range had superaugmented eccentric connectivity topochemical index-3 values of 0.128–0.171. Seventy five percent of the analogues in the active range exhibited anti-HIV-1 activity. The average $IC_{50}$ value of correctly predicted compounds in the active range was found to be only 0.183 μM. This clearly indicates exceptionally high potency of the active range.
- Two inactive ranges—a lower inactive range with index values of $<0.128$ and an upper inactive range with index values of $>0.237$ were observed. Activity of 53 out of 65 compounds in these inactive ranges was predicted correctly.
- A transitional range with index values of $>0.171$ to $<0.237$ was observed. The transitional range indicates gradual transition from active to inactive range and vice versa.
- The ratio of average $IC_{50}$ values of active range and lower inactive range for correctly predicted analogues was found to be 1:203 and ratio of average $IC_{50}$ values of active range and upper inactive range for correctly predicted analogues was found to be 1:71.

## 4. Conclusion

High sensitivity towards presence and relative position of heteroatom(s), exceptionally high discriminating power and negligible degeneracy render all the three conceptualized superaugmented eccentric connectivity topochemical indices extremely beneficial tools for isomer discrimination, similarity/dissimilarity, drug design, quantitative structure–activity/structure–property relationships, lead optimization and combinatorial library design.

Investigations reveal significant correlations of all the three-topochemical indices with anti-HIV-1 activity of 6-arylbenzonitriles. The overall accuracy of prediction for models based on superaugmented eccentric connectivity topochemical indices was ∼81%. High predictability of the proposed models based upon the topochemical indices offer a vast potential for providing lead structures for the development of potent therapeutic agents with regard to anti-HIV-1 activity.

## References

[1] E. Estrada, E. Uriarte, Recent advances on the role of topological indices in drug discovery research, Curr. Med. Chem. 8 (2001) 1573–1588.
[2] K. Roy, Topological descriptors in drug design and modeling studies, Mol. Diver. 8 (2004) 321–323.
[3] S.C. Basak, Use of molecular complexity indices in predictive pharmacology and toxicology: a QSAR approach, Med. Sci. Res. 15 (1987) 605–609.
[4] E. Estrada, O. Ivanciuc, I. Gutman, A. Gutierrez, L. Rodriguez, Extended Wiener indices. A new set of descriptors for quantitative structure–property studies, New J. Chem. 22 (1998) 819–822.
[5] A.T. Balaban, A. Beteringhe, T. Constantinescu, P.A. Filip, O. Ivanciuc, Four new topological indices based on the molecular path code, J. Chem. Inf. Model. 47 (2007) 716–731.
[6] E. Estrada, G. Patlewicz, E. Uriarte, From molecular graphs to drugs. A review on the use of topological indices in drug design and discovery, Indian J. Chem. 42A (2003) 1315–1329.
[7] S.C. Basak, B.D. Gute, G.D. Grunwald, Use of topostructural, topochemical, and geometric parameters in the prediction of vapor pressure: a

hierarchical QSAR approach, J. Chem. Inf. Comput. Sci. 37 (1997) 651–655.
[8] R.A. Musah, The HIV-1 nucleocapsid zinc finger protein as a target of antiretroviral therapy, Curr. Med. Chem. 4 (2004) 1605–1622.
[9] E. De Clercq, Chemotherapeutic approaches to the treatment of the acquired immune deficiency syndrome (AIDS), J. Med. Chem. 29 (1986) 1561–1569.
[10] H. Mitsuya, K.J. Weinhold, P.A. Furman, M.H. St Clair, S.N. Lehrman, R.C. Gallo, D. Bolognesi, D.W. Barry, S. Broder, 3′-Azido-3′-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*, Proc. Natl. Acad. Sci. U.S.A. 82 (1985) 7096–7100.
[11] H. Mitsuya, S. Broder, Strategies for antiviral therapy in AIDS, Nature 325 (1987) 773–778.
[12] D.W. Ludovici, B.L. De Corte, M.J. Kukla, H. Ye, C.Y. Ho, M.A. Lichtenstein, R.W. Kavash, K. Andries, M.P. de Bethune, H. Azijn, R. Pauwels, P.J. Lewi, J. Heeres, L.M. Koymans, M.R. de Jonge, K.J. Van Aken, F.F. Daeyaert, K. Das, E. Arnold, P.A. Janssen, Evolution of anti-HIV drug candidates. Part 3: Diarylpyrimidine (DAPY) analogues, Bioorg. Med. Chem. Lett. 11 (2001) 2235–2239.
[13] D.D. Richman, HIV drug resistance, AIDS Res. Human Retroviruses 8 (1992) 1065–1071.
[14] B.A. Larder, S.D. Kemp, Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to Zidovudine (AZT), Science 246 (1989) 1155–1158.
[15] E. De Clercq, A. Holy, Acyclic nucleoside phosphonates: a key class of antiviral drugs, Nat. Rev. Drug Discov. 4 (2005) 928–940.
[16] J.A. Turpin, Y. Song, J.K. Inman, M. Huang, A. Wallqvist, A. Maynard, D.G. Covell, W.G. Rice, E. Appella, Synthesis and biological properties of novel pyridinioalkanoyl thiolesters (PATE) as anti-HIV-1 agents that target the viral nucleocapsid protein zinc fingers, J. Med. Chem. 42 (1999) 67–86.
[17] E. De Clercq, Novel compounds in preclinical/early clinical development for the treatment of HIV infections, Rev. Med. Virol. 10 (2000) 255–277.
[18] J.P. Moore, M. Stevenson, New targets for inhibitors of HIV-1 replication, Natl. Rev. Mol. Cell. Biol. 1 (2000) 40–49.
[19] J.H. Chan, J.S. Hong, R.N. Hunter III, G.F. Orr, J.R. Cowan, D.B. Sherman, S.M. Sparks, B.E. Reitter, C.W. Andrews III, R.J. Hazen, M.S. Clair, L.R. Boone, R.G. Ferris, K.L. Creech, G.B. Roberts, S.A. Short, K. Weaver, R.J. Ott, J. Ren, A. Hopkins, D.I. Stuart, D.K. Stammers, 2-Amino-6-arylsulfonylbenzonitriles as non-nucleoside reverse transcriptase inhibitors of HIV-1, J. Med. Chem. 44 (2001) 1866–1882.
[20] S. Gupta, M. Singh, A.K. Madan, Predicting anti-HIV activity: computational approach using novel topological descriptor, J. Comput. Aid. Mol. Des. 15 (2000) 671–678.
[21] O. Ivanciuc, T. Ivanciuc, D.J. Klein, W.A. Seitz, A.T. Balaban, Wiener index extension by counting even/odd graph distances, J. Chem. Inf. Comput. Sci. 41 (2001) 536–549.
[22] R. Gozalbes, J. Doucet, F. Derouin, Application of topological descriptors in QSAR and drug design: history and new trends, Curr. Drug Targets Infect. Disord. 2 (2002) 93–102.
[23] A.T. Balaban, Using real numbers as vertex invariants for third-generation topological indexes, J. Chem. Inf. Comput. Sci. 32 (1992) 23–28.
[24] S. Bajaj, S.S. Sambi, A.K. Madan, Model for prediction of anti-HIV activity of 2-pyridinone derivatives using novel topological descriptor, QSAR Comb. Sci. 25 (2006) 813–823.
[25] H. Dureja, A.K. Madan, Prediction of h5-$HT_{2A}$ receptor antagonistic activity of arylindoles: computational approach using topochemical descriptors, J. Mol. Graph. Model. 25 (2006) 373–379.