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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

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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

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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