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Prediction of h5-HT_{2A} receptor antagonistic activity of arylindoles: Computational approach using topochemical descriptors

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Abstract

Relationship between the topochemical indices and h5-HT_{2A} receptor antagonistic activity of arylindoles has been investigated. Three topochemical indices, Wiener's topochemical index – a distance-based topochemical descriptor, molecular connectivity topochemical index – an adjacency-based topochemical descriptor and eccentric connectivity topochemical index – an adjacency-cum-distance based topochemical descriptor, were used for the present investigation. A data set comprising 31 differently substituted arylindoles was selected for the present study. The values of the Wiener's topochemical index, molecular connectivity topochemical index and eccentric connectivity topochemical index were computed for all the analogues involved in the data set using an in-house computer program. 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 h5-HT_{2A} receptor antagonistic activity. Accuracy of prediction was found to vary from a minimum of ~81% to a maximum of ~84%.

Keywords: Topochemical indices; Wiener's topochemical index; Molecular connectivity topochemical index; Eccentric connectivity topochemical index; h5-HT_{2A} receptor antagonistic activity; Schizophrenia

1. Introduction

An important goal in the field of pharmaceutical drug design is the prediction of physicochemical, pharmacological and toxicological properties of molecules directly from their structure [1]. Structure–activity relationships (SARs) are models, which attempt to relate certain structural aspect of molecules to their physicochemical/biological/toxicological properties [2]. The inherent problem in structure–activity relationship (SAR) in quantifying chemical structures can be easily overcome, by molecular topology, by translation of chemical structures into characteristic numerical descriptors [3]. Molecular structure can be represented by planar graphs, $G = (V, E)$, where the vertex set V represents the atoms and edge set E represents the bonds [4]. The topological indices are 2D molecular descriptors whose values are associated with the structural constitution of a chemical compound [5]. Topological indices have several obvious advantages when compared with geometrical, electrostatic, and quantum descriptors: they are computed only from the information contained in the molecular graph; they have a unique value for a particular chemical compound and their calculations require small computational resources [6]. These topological indices facilitate characterization of the molecular structure [7] and can be used for the selection and design of new lead drug molecule [8–12]. The topostructural and topochemical descriptors are collectively referred to as topological descriptors [13]. 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 [14].

Though number of topostructural and topochemical indices has been reported in literature but only few of them have been successfully employed in SARs. Some of the topostructural and topochemical indices, which have been successfully employed in SAR studies include *Hosoya's index* [15], *Randic's molecular connectivity index*, [16,17], *Molecular connectivity topochemical index*, [18,19], *Balaban's index* [20,21], *Wiener's index* [22,23], *Weiner's topochemical index* [24], *Zagreb group parameters* [25–27], *Zagreb topochemical index* [28], *eccentric*

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connectivity index [29–33], *eccentric connectivity topochemical index*, [34] *and eccentric adjacency topochemical index* [35] and s*uperadjacency topochemical index* [36].

Schizophrenia is a severe psychiatric illness, which is characterized by positive symptoms, including delusions, hallucinations and irrational fears, negative symptoms such as social withdrawal and the inability to experience pleasure and cognitive symptoms [37]. The pathophysiology of schizophrenia has involved the dopamine hypothesis and serotonin hypothesis. The dopamine hypothesis arises from the apparent effectiveness of typical antipsychotics in treating the core symptoms of the disease. Typical antipsychotics drugs are brought to act mainly by D_2 receptor blockade, which is believed to be associated with extrapyramidal side effects, such as tardive dyskinesia. The introduction of atypical antipsychotics, which has greater affinity for h5-HT_2 receptor than for hD_2 receptor and shows a much lower incidence of extrapyramidal side effects [38,39]. It has been suggested that drugs may demonstrate atypical features if they have atleast ten times higher affinity for h5-HT_2 receptor than hD_2 receptor [40,41]. Many typical and atypical antipsychotics agents bind with high affinity to 5-HT_2 (particularly 5-HT_{2A}) receptors. Alterations in serotonergic systems have been correlated with specific symptoms of schizophrenia, and novel antipsychotic agents, which function as 5-HT_{2A} antagonists appear to be superior to neuroleptics for treating negative symptoms and treatment-resistant schizophrenia [42,43]. The 5-HT_{2A} receptors are important for many physiologic processes including platelet aggregation, smooth muscle contraction, and the modulation of mood and perception. A large number of pharmaceutical agents mediate their actions, at least in part, by modulating the number and/or activity of 5-HT_{2A} receptors. Drugs with action at 5-HT_{2A} receptors are used in the treatment of many disorders, including schizophrenia, depression, and anxiety disorders [44].

In the present study, relationship of *Wiener's topochemical index* – a distance-based topochemical descriptor, *molecular connectivity topochemical index* – an adjacency-based topochemical descriptor and *eccentric connectivity topochemical index* – an adjacency-cum-distance based topochemical descriptor with h5-HT_{2A} receptor antagonistic activity of arylindoles has been investigated.

2. Methodology

2.1. Calculation of topochemical indices

Wiener's topochemical index (W_c) is a modified form of oldest and widely used distance based topological index—*Wiener's index* [22,23] and this modified index takes into consideration the presence as well as relative position of heteroatoms in a molecular structure. *Wiener's topochemical index* [24] is defined as the sum of the chemical distances between all pairs of vertices in hydrogen suppressed molecular graph, i.e.

$$W_c = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} P_{i_c j_c} \quad (1)$$

where $P_{i_c j_c}$ is the chemical length of the path that contains the least number of edges between vertex i and j in the graph G, n is the maximum possible number of i and j.

Molecular connectivity topochemical index or *atomic molecular connectivity index* (χ^A) is a modified form of a popular and widely used adjacency based topological index—*molecular connectivity index* [16,17] and it takes into consideration the presence as well as relative position of heteroatom(s) in a molecular structure. The *molecular connectivity topochemical index* [18,19] is expressed as

$$\chi^A = \sum_{i=1}^{n} (V_i^c V_j^c)^{-1/2} \quad (2)$$

where, n is the number of vertices, V_i^c and V_j^c are the modified degrees of adjacent vertices i and j forming the edge $\{i, j\}$ in a graph G. The modified degree of a vertex can be obtained from the adjacency matrix by substituting row element corresponding to heteroatom, with relative atomic weight with respect to carbon atom.

Eccentric connectivity topochemical index (ξ_c^c) [34] is defined as the summation of the product of chemical eccentricity and the chemical degree of each vertex in the hydrogen suppressed molecular graph having n vertices, that is

$$\xi_c^c = \sum_{i=1}^{n} (E_{ic} V_{ic}) \quad (3)$$

Where V_{ic} is the chemical degree of vertex i, E_{ic} is the chemical eccentricity of the vertex i and n is the number of the vertices in graph G. *Eccentric connectivity topochemical index* is a modified form of an adjacency-cum-distance based topological index—*eccentric connectivity index* [29–33] and this modified index takes into consideration the presence as well as relative position of heteroatom(s) in a molecular structure.

2.2. Model development

A data set [45] comprising 31 analogues of arylindole was selected for the present investigation. The basic structure for these analogues is depicted in Fig. 1 and various substituents are enlisted in Table 1.

The values of the *Wiener's topochemical index* were computed for each analogue using an in-house computer program. For the selection and evaluation of range specific features, exclusive activity ranges were discovered 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, $\geq$65% = active) [46]. Subsequently, each analogue was assigned a biological activity, which was then compared with the reported [45] h5-HT_{2A} receptor antagonistic activity. The h5-HT_{2A} receptor antagonistic activity was reported quantitatively as K_i values in different concentrations. The analogues possessing K_i values of $\leq$0.5 nM were considered to be active and analogues possessing K_i values of $>$0.5 nM were considered to be inactive for the purpose of present study. The percentage degree of