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Topochemical Models for Prediction of Anti-HIV Activity of 4-Benzyl Pyridinone Derivatives

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ABSTRACT Relationship between topochemical indices and anti-HIV activity of 4-Benzyl pyridinone derivatives has been investigated. The values of molecular connectivity topochemical index (an adjacency based topochemical descriptor) Wiener's topochemical index (a distance based topochemical descriptor) and superadjacency topochemical index (an adjacency cum distance based topochemical descriptor) were calculated for each of the 32 compounds comprising the data set 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 using these models to each of the compounds involved in the dataset which was then compared with the reported anti-HIV activity. Exceptionally high accuracy of prediction was observed using these models. These models offer vast potential for providing lead structures for the development of potent anti-HIV agents.

KEYWORDS Anti-HIV, AIDS, 4-Benzyl pyridinones, Topochemical models, Topological index

INTRODUCTION

Successful applications of multi-drug cocktails using inhibitors of HIV-1 protease and reverse transcriptase have been hailed as milestones in the treatment of AIDS (Turpin et al., 1999). Among the latter, new non-nucleoside reverse transcriptase inhibitors (NNRTI) possibly endowed with better pharmacokinetic profiles, such as capability to inhibit clinically relevant mutants and, hopefully, to minimize the HIV-1 multiplication, are being pursued (De Clercq & Balzarini, 1995; Mai et al., 1999). The NNRTIs bind close to the active site inducing conformational changes that affect the catalytic efficiency of the enzyme (Proudfoot et al., 1995). This enzyme converts viral RNA genome into a double-stranded DNA copy prior to integration into the cell genome, an early event in the replication cycle. Consequently, these agents block acute infection of cells but are minimally active in chronically infected ones (Hayden, 1996). Examples of NNRTIs include PETT compounds (Bell et al., 1995), TIBO compounds (Pauwels et al.,

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1990), HEPT derivatives (Miyasaka et al., 1989), BHAP analogs (Romero et al., 1991) and 2-Pyridinones (Saari et al., 1992) etc. Rapid development of drug resistant variants is one of the major drawbacks of this class of drugs. Therefore, 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 (De Clercq, 2000; Moore & Stevenson, 2000). Anti-HIV therapy also requires faster introduction of newer agents to fight the epidemic because each day approximately 14,000 new infections are occurring and AIDS is now the leading cause of death in Sub-Saharan Africa and the fourth-biggest killer globally (http://www.world bank.org).

Drug discovery usually begins with the identification of lead structure, followed by synthesis and testing of hundreds of compounds which involve a lot of time and resources. The critical step in drug discovery remains the identification and optimization of lead compounds in a rapid and cost effective way. Computational techniques have advanced rapidly over the past decade and accordingly have played a major role in the development of a number of drugs now on the market or going through clinical trials (Estrada et al., 2003). Among the computational techniques used in drug design, topological indices (TIs) occupy an eminent place. A systematic approach for drug design and discovery using TIs has been applied by the Galvez group from the mid 1990s (Estrada et al., 2003). TOPSMODE approach is another strategy using TIs for drug design and quantitative structure-activity relationship (QSAR) (Estrada et al., 2000). TIs have been used in similarity/dissimilarity studies for synthesizing and screening of combinatorial libraries as well as lead identification searching from large structural databases (Estrada et al., 2002; Willett et al., 1998). In addition, TIs have been used actively for deriving QSAR/topological models (Bajaj et al., 2004a; Gupta et al., 2001a, 2002; Lather & Madan, 2004; Mendiratta & Madan, 1994; Quigley & Naughton, 2002; Sardana & Madan, 2002a, 2002b; Sharma et al., 1997), creating combinatorial libraries (Gallop et al., 1994), and for rational design of targeted combinatorial library (Zheng et al., 1998). Recent advances in this area have been by combining simplicity of TIs with the powerful statistical tool applied in 3D QSAR, namely PLS (Cho et al.), introduction and use of chirality topological indices (Golbraikh et al., 2001), and application of artificial neural networking (ANN) to TIs QSAR (Huuskonen et al., 1998).

One of the limitations of the TIs is their inability to take into consideration the presence and relative position of heteroatom. Introduction of topochemical indices has been able to overcome this handicap of the TIs. When a single number represents a graph invariant, it is known as topological index or topological descriptor. 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., present within the 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. Topochemical indices that have been reported and used for QSAR studies include molecular connectivity topochemical index (Dureja, 2005; Goel & Madan, 1995; Gupta et al., 2001b), eccentric adjacency topochemical index (Gupta et al., 2003), Wiener's topochemical index (Bajaj et al., 2004b), and Superadjacency topochemical index (Bajaj et al., 2004c). In the present study three topochemical indices, i.e., atomic molecular connectivity index (an adjacency based topochemical descriptor), Wiener's topochemical index (a distance based topochemical descriptor), and superadjacency index (an adjacency cum distance based topochemical descriptor) have been used for the development of models for prediction of anti-HIV-1 activity of 4-benzyl pyridinone derivatives.

METHODOLOGY

Calculation of Topochemical Indices

Molecular Connectivity Topochemical Index

Molecular connectivity topochemical index is the modification of path-one molecular connectivity index. It takes into consideration the influence of heteroatom(s) and is defined as the summation of the modified bond values of adjacent vertices for all edges

in the hydrogen suppressed molecular graph. It is denoted by χ^A and is expressed as

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

where n is the number of vertices, v_i and v_j are the modified degrees of adjacent vertices, and 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(s) with relative atomic weight with respect to carbon atom (Dureja, 2005; Goel & Madan, 1995; Gupta et al., 2001b).

Wiener's Topochemical Index

Wiener's topochemical index is defined as the sum of the chemical distances between all the pairs of vertices in a hydrogen suppressed molecular graph, that is

$$W_c = \frac{1}{2} \sum_{i=1}^{n} \sum_{j=1}^{n} P_{ij}^c$$

where P_{ij}^c is the chemical length of the path that contains the least number of edges between vertex i and vertex j in the graph G and n is the maximum possible number of i and j. Wiener's topochemical index (W_c) can be easily calculated from the chemical distance matrix of a hydrogen suppressed molecular structure. This matrix is obtained by substituting row elements corresponding to heteroatom(s) with relative atomic weight with respect to carbon atom (Bajaj et al., 2004b).

Superadjacency Topochemical Index

The superadjacency topochemical index is denoted by $\int^{Ac}$ and is defined as the sum of the products of the concerned vertex chemical degree and the sum of adjacent vertex chemical degrees divided by the chemical eccentricity of the concerned vertex, over all the vertices in the hydrogen suppressed molecular graph. It is expressed as

$$\int^{Ac} = \sum_{i=1}^{n} \frac{\deg V_i^c * S_{ic}}{E_{ic}}$$

$$S_{ic} = \sum \deg V_j^c$$

where S_{ic} is the sum of chemical degrees of all vertices (v_j) adjacent to vertex i, and n is the number of vertices in graph G.

For a molecular graph (G), $v_1, v_2, \ldots v_n$ are vertices, the number of first neighbors of a vertex v_i is the chemical degree of this vertex and is denoted by $\deg(v_{ic})$. The chemical distance dc (v_i, v_j|G) between the vertices v_i and v_j of G is the length of the shortest path connecting v_i to v_j. Chemical eccentricity E_{ic} of vertex v_i in graph G is the length of the shortest path from v_i to vertex v_j that is farthest from v_i ($E_{ic} = \max dc$ (v_i, v_j); j|G). Superadjacency topochemical index is calculated from the chemical distance matrix (D^c), the chemical adjacency matrix (A^c), and a new matrix, the additive chemical adjacency matrix ($A^{\alpha c}$), obtained by modifying A^c. Chemical distance matrix is utilized for deriving chemical eccentricity while chemical adjacency matrix is utilized for deriving chemical degree of vertices. When non-zero row elements in chemical adjacency matrix represent the chemical degree of corresponding vertex in a molecular graph, the matrix may be defined as the additive chemical adjacency matrix. This matrix is utilized for deriving S_{ic} for the corresponding vertex (Bajaj et al., 2004c).

Model Development and Analysis

A dataset comprising of 32 4-benzyl pyridinone derivatives (Dolle et al., 2000) having anti-HIV activity was selected for the development of model. The basic structure of these compounds is presented in Fig. 1. The values of molecular connectivity topochemical index, Wiener's topochemical index, and superadjacency topochemical index of each compound involved in the data set was calculated using an in-house computer program. The resultant data was analyzed and active ranges were identified by maximization of the moving average with respect to active compounds (Bajaj et al., 2004a, 2004c; Gupta et al., 2001a). Subsequently, each analog was assigned a biological activity using these models which was then compared with the reported activity. The activity of these compounds was reported in terms of inhibitory concentration (IC_{50}) expressed in nano moles (nM). The activity was determined on HIV-1 Lai wild in CEM-SS cells. The analogs

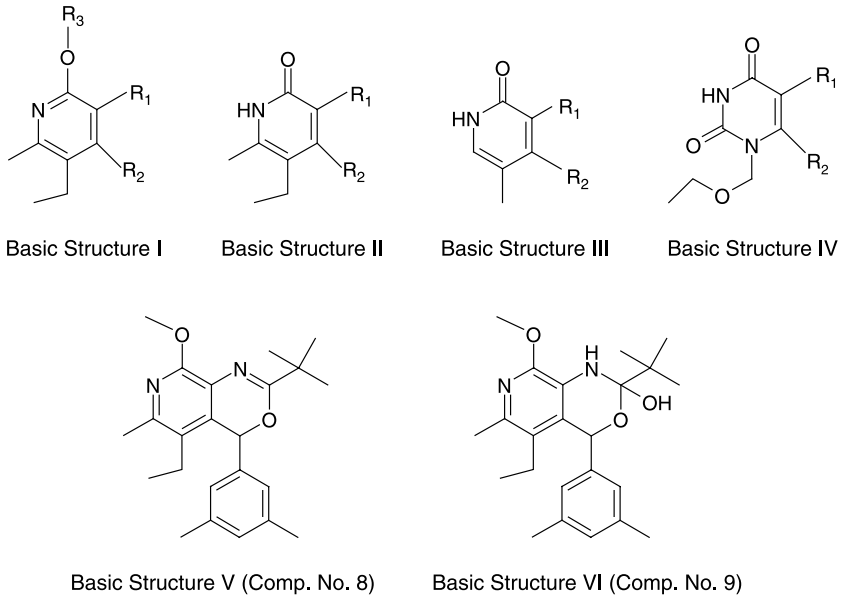


FIGURE 1 **Basic Structures of 4-Benzyl Pyridinone Derivatives.**

exhibiting $IC_{50}<100$ nM were considered to be active for the purpose of this study. The percent degree of prediction for each range was calculated from the ratio of the number of compounds for which activity was predicted correctly to that of total number of compounds present in the respective range. The overall degree of prediction was obtained from the ratio of total number of compounds with correctly predicted activity to that of total number of analogues present in both active and inactive ranges. The percent classification was obtained from the ratio of number of compounds present in active and inactive ranges to the total number of compounds in the data set. The results have been summarized in Table 2.

RESULTS

Retrofit analysis of the data in Tables 1 and 2 reveal the following information with regard to the corresponding indices.

Molecular connectivity topochemical index

- Out of 32 compounds, 29 (90.62%) were predicted correctly with respect to anti-HIV-1 activity.
- The active range had molecular connectivity topochemical index values from 10.08 to 11.05. All the eight compounds in the active range were predicted correctly. The average IC_{50} (nM) of the correctly predicted compounds was only 22.675.
- The lower inactive range had molecular connectivity topochemical index values less than 10.08 and the upper inactive range had molecular connectivity topochemical index values greater than 11.05. Seven out of 10 compounds (70%) in the lower inactive range were predicted correctly while all the 14 compounds in the upper inactive range were predicted correctly. The average IC_{50} (nM) of the correctly predicted compounds in both the inactive ranges was 17175.71.

Wiener's topochemical index:

- Out of 32 compounds, 22 were classified as active or inactive. All 22 (100%) compounds were predicted correctly with respect to anti-HIV-1 activity.
- The active range had Wiener's topochemical index values from 995.18 to 1197.02. All five compounds in the active range were predicted correctly. The average IC_{50} (nM) of the correctly predicted compounds was 22.560.
- The lower inactive range had Wiener's topochemical index values less than 629.86. All the compounds (100%) in the lower inactive range were predicted correctly. The upper inactive range had Wiener's topochemical index values greater than 1443.54. All the compounds (100%) in the upper inactive range were predicted correctly. The average IC_{50} (nM) of the correctly predicted

TABLE 1 Index Values and Comparison of Assigned and Reported Anti-HIV Activity of 4-Benzyl Pyridinone Derivatives

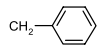
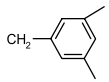
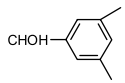
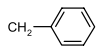
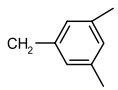
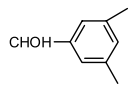
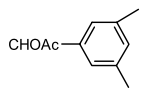
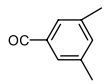
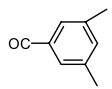
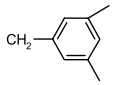
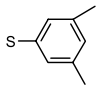
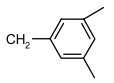
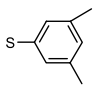
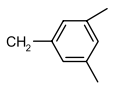
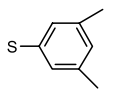
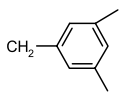
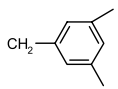
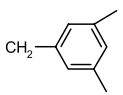
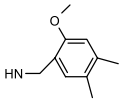
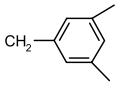
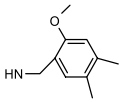
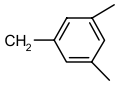
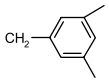
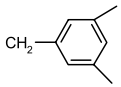
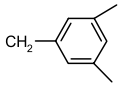
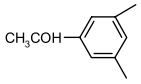
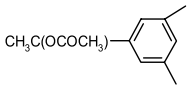
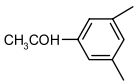
							Anti-HIV activity			
							Assigned			
Comp. no.	Basic str.	Substituent R_1	R_2	$^{\chi}A$	W_C	$\int^{Ac}$	$^{\chi}A$	W_C	$\int^{Ac}$	Reported
1	I	$NHCOC(CH_3)_3$	H	7.950	629.852	37.139	–	–	–	–
2	I	$NHCOC(CH_3)_3$		11.436	1444.697	43.087	–	–	–	–
3	I	$NHCOC(CH_3)_3$		12.223	1774.367	46.088	–	–	–	–
4	I	$NHCOC(CH_3)_3$		12.587	1900.697	49.722	–	–	–	–
5	II	NH_2		8.465	592.337	35.531	–	–	–	–
6	II	NH_2		9.252	789.004	39.271	–	±	+	+
7	II	NH_2		9.616	868.668	44.061	–	±	–	–
8	V	—	—	12.270	1640.497	55.865	–	–	–	–
9	VI	—	—	12.572	1774.660	60.500	–	–	–	–
10	I	$NHCOC(CH_3)_3$		13.840	2442.67	54.248	–	–	–	–
11	I	$NHCOC(CH_3)_3$		12.587	1900.697	49.722	–	–	–	–
12	II	NH_2		9.616	868.668	44.061	–	±	–	+

TABLE 1 Continued

Comp. no.	Basic str.	Substituent R_1	R_2	$^{1}\chi^{A}$	W_C	$\int^{Ac}$	Anti-HIV activity: Assigned $^{1}\chi^{A}$	Assigned W_C	Assigned $\int^{Ac}$	Reported
13	II	$NHCOCH_2CH_3$		11.085	1304.86	40.836	–	±	+	–
14	III	$NHCOCH_2CH_3$		9.682	1255.062	36.850	–	±	–	–
15	II	$NHCOCH_3$		10.535	1153.187	41.119	+	+	+	+
16	II	$NHCOCH_3$		10.081	1358.228	39.986	+	±	+	+
17	II	NHCHO		10.167	1024.514	39.547	+	+	+	+
18	III	NHCHO		8.764	977.045	35.635	–	±	–	–
19	II	$NHCH_3$		9.742	894.511	40.871	–	±	+	+
20	IV	CH_2CH_3		10.518	1197.017	38.978	+	+	+	+
21	II	$NHCO_2CH_2CH_3$		11.438	1499.181	38.077	–	–	–	–

22	III	$NHCO_2CH_2CH_3$		10.035	1443.553	36.234	–	–	–	–
23	II			14.376	2732.227	40.617	–	–	+	–
24	II		H	10.103	1146.198	32.719	+	+	–	+
25	II	$N(CH_3)_2$		10.232	995.181	42.705	+	+	+	+
26	IV	$HC(CH_3)_2$		10.891	1318.351	40.843	+	±	+	+
27	II	$NHCOCH_2NH_2Boc$		13.891	2999.904	35.461	–	–	–	–
28	II	$NHCOCH_2NH_2$		11.043	1306.780	40.400	+	±	+	+
29	I	$NHCOC(CH_3)_3$		12.922	2024.699	53.303	–	–	–	–
30	I	$NHCOCH_3$		13.513	2170.157	54.435	–	–	–	–
31	II	$NHCOC(CH_3)_3$		12.466	1851.705	51.747	–	–	–	–
32	II	NH_2	H	4.979	152.003	29.665	–	–	–	–

+Active compounds (compounds having $IC_{50}<100$). –Inactive compounds and ±compounds in transitional range.

TABLE 2 Proposed Models for Prediction of Anti-HIV Activity of 4-Benzyl Pyridinone Derivatives

Model index	Nature of range in proposed model	Index value	Number of compounds falling in the range		Percent accuracy	Average IC_{50} (nM)		Total accuracy of prediction	Percent classification
			Total	Correct		Total	Correct		
χ^A	Lower inactive	<10.08	10	7	70.0	18728.30	26747.14	90.62	100
	Active	10.08–11.05	8	8	100	22.68	22.68		
	Upper inactive	>11.05	14	14	100	12390.00	12390.00		
W_c	Lower inactive	<629.86	3	3	100	43576.67	43576.67	100	68.75
	Lower transitional	629.86–995.17	5	N.A.	N.A.	N.A.	N.A.		
	Active	995.18–1197.02	5	5	100	22.56	22.56		
	Upper transitional	1197.03–1443.54	5	N.A.	N.A.	N.A.	N.A.		
	Upper inactive	>1443.54	14	14	100	12597.14	12597.14		
$\int^{Ac}$	Lower inactive	<38.97	9	8	88.9	21488.67	24173.75	87.50	100
	Active	38.97–42.71	11	9	81.8	529.13	24.49		
	Upper inactive	>42.71	12	11	91.7	13475.50	14700.00		

compounds in both the inactive ranges was 18064.12.
- The active range was ideally bracketed by two transitional ranges. A total of 10 compounds were present in both the transitional ranges.

Superadjacency topochemical index:

- All the 32 compounds were classified into active and inactive ranges. Out of these, 28 (87.5%) were predicted correctly with respect to anti-HIV-1 activity.
- The active range had superadjacency topochemical index values from 38.970 to 42.710. Nine out of 11 compounds (81.8%) in the active range were predicted correctly. The IC_{50} (nM) of the correctly predicted compounds in the active range was only 24.488.
- The lower inactive range had superadjacency topochemical index values less than 38.970 and the upper inactive range had superadjacency topochemical index values greater than 42.71. Nineteen out of 21 compounds (95.24%) in both the inactive ranges were predicted correctly. The average IC_{50} (nM) in both the inactive range was 18688.95.

DISCUSSION

Mathematical-topological methods occupy an eminent place in the field of prediction of properties and activities of chemical compounds, and even materials. These methods, known as QSPR/QSAR, are normally, but not always, based upon graph-theoretical descriptors, where molecules are seen as graphs, i.e., as a set of vertices attached to each other by a set of non-metrical connections (Pogliani, 2003). This approach is seen as an important alternative to computer-aided molecular design methods (Rouvray, 1993). The basis for these methods is that there exists a correlation between the physicochemical properties like lipophilicity and aqueous solubility as well as biological activity of drug molecules and the topological indices. These theoretical indices are numbers that describe the structural information of molecules through graph-theoretical invariants (Hansen & Jurs, 1988). A topological and/or topochemical index are not always correlated with the biological activities of drug molecules, but one has to look for the index that correlates best with the biological activity of that set of compounds and, subsequently, develop the best fitting model. In the present investigation, three topochemical indices were selected for development of models. The idea behind choosing these three indices was that these indices provide structural information on three different concepts, since molecular connectivity topochemical index is based upon adjacency or connectivity of atoms within a molecule. Wiener's topochemical index is based upon inter-atomic distances, and the third superadjacency topochemical index is based upon the combination of both adjacency as well as inter-atomic distance. All three indices have demonstrated excellent correlation with the anti-HIV activity of 4-benzyl pyridinone derivatives. These compounds have been reported to be potent and selective NNRTIs of HIV-1 and can be considered as hybrid molecules of well-known anti-HIV group of compounds, HEPT, and pyridinone. This set of compounds was especially developed to obtain more chemically stable analogues. The most active compounds in this series have been reported to have IC_{50} values ranging from 0.2 to 6 nM and one of the compounds was capable of inhibiting the virus resistant to nevirapine with an IC_{50} of 40 nM (Dolle et al., 2000). Therefore, this series of compounds has vast potential for development of potent anti-HIV agents.

The model based upon molecular connectivity topochemical index, as well as the one based upon superadjacency topochemical index, comprises of three ranges, one active range sandwiched between two inactive ranges. Whereas in both these models the classification was 100%, i.e., all the compounds were classified as either active or inactive, the accuracy of prediction of the model based upon the molecular connectivity topochemical index was marginally higher. The model based upon Wiener's topochemical index comprises of five ranges with the active range having been separated from the two inactive ranges by two transitional ranges. This indicates that, in this model, the transition of activity over the index value is gradual and, therefore, the active and inactive ranges are highly specific. Though the accuracy of prediction using model based upon Wiener's topochemical index was surprisingly found to be 100%, the classification was only 69%. Since the dataset comprised of 32 compounds only, it was not divided into training and test sets for validation of predictability of the models.

In depth analysis of the structure of the compounds present in the active ranges of these models reveals that, in general, the compounds containing tri-methyl moiety in functional group at R_1 are inactive. It also appears that the presence of terminal nitrogen or carbon atoms spatially near the oxygen atom, i.e., ketonic function either in the main ring or in the function group at R_1, plays an important role in the RT inhibition. It may also be one of the reasons why the compounds having methyl group at R_3 (example compound no. 30, Basic structure I), are inactive. This structure-activity relationship and the predictability offered by these models makes them useful for further development of this series of anti-HIV agents, and they may be helpful in predicting the activity of compounds before having been synthesized.

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