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Topological models for the prediction of anti-HIV activity of dihydro (alkylthio) (naphthylmethyl) oxopyrimidines

Viney Lather and A. K. Madan*

Faculty of Pharmaceutical Sciences, M. D. University, Rohtak 124001, India

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Abstract—Relationship between the topological indices and anti-HIV activity of Dihydro (alkylthio) (naphthylmethyl) oxopyrimidines has been investigated. Three topological indices—the *Wiener's index*—a distance-based topological index, *molecular connectivity index*—an adjacency based topological index and *eccentric connectivity index*—an adjacency-cum-distance based topological index were used for the present investigations. A data set comprising of 67 analogues of dihydro (alkylthio) (naphthylmethyl) oxopyrimidine (S-DABO) was selected for the present investigations. The values of the *Wiener's index*, *molecular connectivity index* and *eccentric connectivity index* for each of the 67 compounds comprising the data set were computed using an in house computer program. Resultant data were subsequently analyzed and suitable models were developed after identification of active ranges. Subsequently, a biological activity was assigned to each compound using these models, which was then compared with the reported anti-HIV activity. The use of models based upon these topological indices resulted in prediction of anti-HIV activity with an accuracy ranging from 86% to 89%.

1. Introduction

Since the onset of acquired immunodeficiency syndrome (AIDS) about 15 years ago the virus has infected more than 47 million people in the world. With more than 2.2 million deaths, AIDS has now become the fourth leading cause of mortality and its impact is going to increase (World Health Organization web report on the global HIV/AIDS epidemic, 1998).[1] Various compounds have been reported by De Clercq to inhibit the replication of causative retrovirus called human immunodeficiency virus type 1 (HIV-1), in vitro.[2] A thymidine derivative 3′-azido-3′-deoxy-thymidine (AZT) is clinically effective in the treatment of AIDS but is associated with the side effects like bone marrow suppression besides emergence of AZT-resistant HIV variants. A purine dideoxy nucleoside, 2′,3′-dideoxyinosine (DDI) is used as an alternate drug for the patients who do not tolerate AZT, but it also has unfavourable side effects.

The enzyme reverse transcriptase of HIV-1 is an essential enzyme required for the catalytic conversion of viral RNA into proviral DNA and, therefore, is the target for antiviral therapy against AIDS. AZT and DDI act as inhibitors of viral reverse transcriptase after phosphorylation by cellular kinases.[3] Unlike the nucleosides that act at the catalytic site of HIV reverse transcriptase (RT) by terminating DNA synthesis, NNRTIs bind in a region of the enzyme, which is approximately 10 Å away from the catalytic site. Their binding appears to result in a distortion of the catalytic site because of changes in the position of the key aspartic residues, which affects the ability of the enzyme to carry out its catalytic functions.[4] NNRTIs do not require anabolism for activation. Since they are not analogues of natural compounds and do not utilize the biochemical machinery of the host cells, NNRTIs usually manifest different toxicity profiles. Side effects are usually milder than those resulting from treatment with nucleosides.[5]

Combination therapy avoids or delays emergence of resistant viral strains, particularly when such pressure comes from potent drugs with different mechanisms of inhibition. Such multiple drug treatment approach has indeed contributed to the declining morbidity and mortality among HIV-infected patients.[6,7] Yet because of a high pill burden, coupled with the high cost of treatment and toxicity profile, much still remains to be done to advance HIV chemotherapy.

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* Corresponding author. Tel.: +91 1262 272535; e-mail: madan_ak@yahoo.com

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A contemporary trend in mathematical chemistry and chemical graph theory is the characterization of molecular structure using graph theoretical invariants.[8,9] In particular there is an upsurge of interest in the use of topological indices in formulating quantitative structure–property/activity/toxicity relationships (QSPRs/QSARs/QSTRs) of chemicals, defining structural similarity of molecules and clustering of large databases of chemicals into smaller subsets for screening in drug discovery as well as the biological activity assessment.[10]

Molecules can be looked upon as 'assembled entities' in which various constituent parts, viz., atoms, are connected to form a particular chemical species. The basic combinatorial aspect of such an assemblage may be represented by a set (of atoms) with a binary relation defined on it. A graph $G = (V, E)$ where V represents a non-empty set of atoms and the set E symbolizes some type of bonds (usually covalent), depicts the fundamental connectivity of atoms which determines many properties of molecular systems.[11]

Mathematical characterization of molecular graphs can be conveniently accomplished by graph invariants.[12,13] A graph invariant is a graph theoretic property or parameter which is either identical or has the same value for isomorphic graphs. A graph invariant may be a polynomial, a sequence of numbers or a single numerical index. A single numerical index characterizing a molecular graph has been called a topological index (TI).[14] A topological index calculated for a molecular graph is a numerical quantifier of molecular topology. TIs are sensitive to such structural features as size, shape, bonding patterns, symmetry, content of heteroatoms as well as the degree of complexity of atomic neighbourhoods.

Since structure of a compound depends on connectivity of its constituent atoms, topological descriptors derived from information based upon connectivity can reveal the role of structural or sub-structural information of a molecule in estimating biological activity. Topological descriptors developed for predicting physicochemical properties and biological activities of chemical substances can be used for drug design.[15–17]

In the present study, relationship of *Wiener's index*—a distance-based topological descriptor, *molecular connectivity index*—an adjacency-based topological descriptor and *eccentric connectivity index*—an adjacency-cum-distance based topological descriptor with the anti-HIV activity of dihydro (alkylthio) (naphthylmethyl) oxopyrimidines has been investigated.

2. Methodology

2.1. Calculation of topological indices

The *Wiener's index*,[18,19] a well-known distance-based topological index is defined as half sum of the distances between all the pairs of vertices in a hydrogen-suppressed molecular graph, that is

$$W = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} P_{ij} \tag{1}$$

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

The *molecular connectivity index*,[20] an adjacency based topological index proposed by Randic is denoted by χ and is defined as the sum over all the edges (ij) as per following:

$$\chi = \sum_{\substack{i=1\\ j=1}}^{n} (V_i V_j)^{-1/2} \tag{2}$$

where V_i and V_j are the degrees of adjacent vertices i and j and n is the number of vertices in a hydrogen suppressed molecular structure.

The *eccentric connectivity index*,[21] an adjacency-cum-distance based topological index denoted by ξ^c is defined as the summation of the product of eccentricity and the degree of each vertex in the hydrogen suppressed molecular graph having n vertices

$$\xi^c = \sum_{i=1}^{n} (E_i * V_i) \tag{3}$$

where V_i is the degree of vertex i, E_i is the eccentricity of the vertex i and n is the number of the vertices in graph G. The eccentricity E_i of a vertex i in a graph G is the path length from vertex i to vertex j that is farthest from i ($E_i = \max\ d(ij)$; $j \varepsilon G$); the eccentric connectivity index takes into consideration the eccentricity as well as valency of the vertices in a hydrogen-suppressed graph.

3. Model development

A data set comprising of 67 analogues of dihydro (alkylthio) (naphthylmethyl) oxopyrimidines (S-DABOs) was selected for the present investigations.[22] The basic structure for these analogues is depicted in Figure 1 and var-

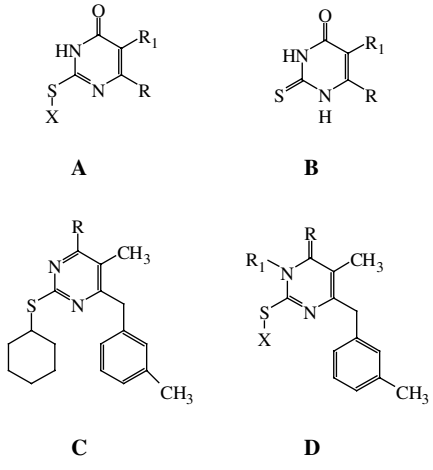

Figure 1. Basic structures of S-DABO analogues.

ious substituents enlisted in Table 1. The data set comprised of both active and inactive compounds.

The values of the *Wiener's 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. This can be easily accomplished by firstly plotting relationship between index values and the inhibitory activity 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% = inactive).[23] Suitable models were developed after identification of the active ranges. Subsequently, each analogue was assigned a biological activity using this model, which was then compared with the reported anti-HIV activity. The anti-HIV activity was reported quantitatively as effective concentration required to achieve 50% protection of MT-4 cells from the HIV-1 induced cytopathogenicity (EC_{50}). The analogues possessing EC_{50} values of <10 μM were considered to be active and analogues possessing EC_{50} values of >10 μM were considered to be inactive for the purpose of present study. The cytotoxic activity reported for 67 analogues was defined as cytotoxic concentration required to reduce the viability of mock-infected cells by 50% (CC_{50}). The selectivity index (SI) was defined as quotient of CC_{50} and EC_{50}. The analogues having SI value ⩾20 were considered to be safe and those having a value <20 were considered to be toxic. SI data in Table 1 was either reported in Ref. 22 or calculated from the values of CC_{50} and EC_{50} reported in Ref. 22. The percentage degree of prediction of a particular range was derived from the ratio of the number of compounds predicted correctly to the total number of compounds present in that range. The overall degree of prediction was derived from the ratio of the total number of compounds predicted correctly to that of the total number of compounds present in both the active and inactive ranges. Aforementioned procedure was similarly adopted for *molecular connectivity index*, χ and *eccentric connectivity index*, ξ^c. The results are summarized in Tables 1 and 2.

4. Results

Chemists have long relied on visual perception, to relate various aspects of constitutional graphs and observable physical, chemical or biological phenomenon. The quantitative understanding of structural basis requires mathematical characterization of complexity or symmetry of chemical compounds. Graph theory accomplishes this by converting constitutional graphs into adjacency/distance matrices that are the basis of characteristic numerical descriptors.[24]

Relationship of topological indices, that is, *Wiener's index*—a distance-based topological descriptor, *molecular connectivity index*—an adjacency-based topological descriptor and *eccentric connectivity index*—an adjacency-cum-distance based topological descriptor with the anti-HIV activity of dihydro (alkylthio) (naphthylmethyl) oxopyrimidines has been investigated in the present studies by the development of suitable models.

Retrofit analysis of Tables 1 and 2 reveals the following information with regard to different models used in the present study.

Model based upon *Wiener's index*:

- A total of 52 out of 59 analogues were classified correctly in both the active and inactive ranges. The overall accuracy of prediction was found to be 88.13% with regard to anti-HIV activity.
- The active range had a *Wiener's index* value of 1396–1638. Eight out of nine analogues in the active range exhibited the anti-HIV activity. The average EC_{50} value was found to be 4.6 μM, indicating the presence of highly active compounds in the active range.
- The average SI value of the active range was found to be 64.8 indicating safety of the active analogues. Eight out of nine analogues in the active range had a SI value more than 20.
- Presence of a transitional range having a *Wiener's index* value of 1258–1391 indicated the gradual change from the inactive to active range. The average EC_{50} value was found to be 68.4 μM for the analogues in the transitional range. The average SI value was found to be 156.5.

Model based upon *molecular connectivity index*:

- A total of 47 out of 53 analogues were classified correctly in both the active and inactive ranges. The overall accuracy was found to be 88.7% with regard to anti-HIV activity.
- The active range had a *molecular connectivity index* value of 11.69–12.276. Six out of seven analogues in the active range exhibited anti-HIV activity. The average EC_{50} value was found to be 5.07 μM, indicating the presence of highly active compounds in the active range.
- The average SI value was found to be 71.7, indicating very low toxicity of the compounds in the active range. Six out of seven analogues in the active range had a SI value more than 20.
- Presence of a transitional range having a *molecular connectivity index* value of 11.097–11.652 indicated the gradual change from the inactive to active range. The average EC_{50} value was found to be 64.4 μM for the analogues in the transitional range. The average SI value was found to be 64.4.

Model based upon *eccentric connectivity index*:

- A total of 51 out of 59 analogues were classified correctly in both the active and inactive ranges. The overall accuracy was found to be 86.44% with regard to anti-HIV activity.
- The active range had an *eccentric connectivity index* value of 494–519. All the compounds in the active range exhibited anti-HIV activity. The average

Table 1. Relationship of *Wiener's index*, *molecular connectivity index* and *eccentric connectivity index* with anti-HIV activity

Compd No.	R	R_1	X	W	χ	ξ^c	Anti-HIV activity				SI
							Predicted			Reported	
							W	χ	ξ^c		
A_1	Phenyl	H	sec-Butyl	641	8.648	285	–	–	–	–	1
A_2	Phenyl	H	Cyclopentyl	727	9.31	322	–	–	–	–	1
A_3	Phenyl	H	Cyclohexyl	847	9.81	368	–	–	–	–	1
A_4	Phenyl	Me	sec-Butyl	720	9.075	300	–	–	–	–	1
A_5	Phenyl	Me	Cyclopentyl	813	9.737	337	–	–	–	–	1
A_6	Phenyl	Me	Cyclohexyl	942	10.237	385	–	–	–	–	1.4
A_7	Phenylethyl	H	sec-Butyl	930	9.631	381	–	–	–	–	1.4
A_8	Phenylethyl	H	Cyclopentyl	1041	10.293	426	–	–	–	–	1.9
A_9	Phenylethyl	H	Cyclohexyl	1190	10.793	474	–	–	–	–	6
A_{10}	Phenylethyl	Me	sec-Butyl	1028	10.059	396	–	–	–	–	16
A_{11}	Phenylethyl	Me	Cyclopentyl	1146	10.72	441	–	–	–	–	11
A_{12}	Phenylethyl	Me	Cyclohexyl	1304	11.22	491	±	±	–	–	6
A_{13}	Phenoxymethyl	H	sec-Butyl	930	9.631	381	–	–	–	–	2
A_{14}	Phenoxymethyl	H	Cyclopentyl	1041	10.293	426	–	–	–	–	1
A_{15}	Phenoxymethyl	H	Cyclohexyl	1190	10.793	474	–	–	–	–	7
A_{16}	Phenoxymethyl	Me	sec-Butyl	1028	10.059	396	–	–	–	+	13
A_{17}	Phenoxymethyl	Me	Cyclopentyl	1146	10.72	441	–	–	–	–	14
A_{18}	Phenoxymethyl	Me	Cyclohexyl	1304	11.22	491	±	±	–	–	5.4
A_{19}	(Phenylthio)methyl	H	sec-Butyl	930	9.631	381	–	–	–	–	4.5
A_{20}	(Phenylthio)methyl	H	Cyclopentyl	1041	10.293	426	–	–	–	–	9.4
A_{21}	(Phenylthio)methyl	H	Cyclohexyl	1190	10.793	474	–	–	–	–	3.3
A_{22}	(Phenylthio)methyl	Me	sec-Butyl	1028	10.059	396	–	–	–	–	2
A_{23}	(Phenylthio)methyl	Me	Cyclopentyl	1146	10.72	441	–	–	–	–	2
A_{24}	(Phenylthio)methyl	Me	Cyclohexyl	1304	11.22	491	±	±	–	–	1
A_{25}	Me	Benzyl	sec-Butyl	888	9.559	369	–	–	–	–	1
A_{26}	Me	Benzyl	Cyclopentyl	999	10.22	414	–	–	–	–	1
A_{27}	Me	Benzyl	Cyclohexyl	1148	10.72	466	–	–	–	–	1
A_{28}	*n*-Propyl	H	sec-Butyl	402	7.113	201	–	–	–	–	1
A_{29}	*n*-Propyl	H	Cyclopentyl	554	8.275	270	–	–	–	–	300
A_{30}	1-Naphthylmethyl	H	Isopropyl	1083	10.614	409	–	–	–	+	909
A_{31}	1-Naphthylmethyl	H	sec-Butyl	1258	11.114	459	±	±	–	+	34
A_{32}	1-Naphthylmethyl	H	2-Pentyl	1420	11.652	512	+	±	+	+	50
A_{33}	1-Naphthylmethyl	H	3-Pentyl	1401	11.69	480	+	+	–	+	150
A_{34}	1-Naphthylmethyl	H	Cyclopentyl	1396	11.776	504	+	+	+	+	96
A_{35}	1-Naphthylmethyl	H	Cyclohexyl	1578	12.276	560	+	+	±	+	100
A_{36}	1-Naphthylmethyl	H	Cycloheptyl	1763	12.776	586	–	–	±	+	24
A_{37}	1-Naphthylmethyl	H	Benzyl	1820	12.776	623	–	–	–	–	1
A_{38}	1-Naphthylmethyl	H	*n*-Undecyl	3598	15.258	1078	–	–	–	–	300
A_{39}	1-Naphthylmethyl	Me	sec-Butyl	1374	11.542	474		±	–	+	50
A_{40}	1-Naphthylmethyl	Me	Cyclopentyl	1519	12.204	519	+	+	+	+	4.7
A_{41}	1-Naphthylmethyl	Me	Cyclohexyl	1710	12.704	577	–	–	±	–	14
A_{42}	2-Naphthylmethyl	H	sec-Butyl	1310	11.097	494	±	±	+	+	8.1
A_{43}	2-Naphthylmethyl	H	Cyclopentyl	1452	11.759	543	+	+	±	+	128
A_{44}	2-Naphthylmethyl	H	Cyclohexyl	1638	12.259	596	+	+	±	+	47
A_{45}	2-Naphthylmethyl	Me	sec-Butyl	1430	11.525	511	+	±	+	+	20
A_{46}	2-Naphthylmethyl	Me	Cyclopentyl	1579	12.187	560	+	+	±	–	2.4
A_{47}	2-Naphthylmethyl	Me	Cyclohexyl	1774	12.687	613	–	–	–	–	1
B_1	Phenoxymethyl	H	—	485	7.737	246	–	–	–	–	1
B_2	(Phenylthio)methyl	H	—	485	7.737	246	–	–	–	–	1
B_3	1-Naphthylmethyl	H	—	702	9.22	300	–	–	–	–	1
B_4	2-Naphthylmethyl	H	—	738	9.204	329	–	–	–	–	1
B_5	Phenylethyl	Me	—	485	7.737	246	–	–	–	–	1
B_6	Phenoxymethyl	Me	—	554	8.165	261	–	–	–	–	1
B_7	(Phenylthio)methyl	Me	—	554	8.165	261	–	–	–	–	1
B_8	1-Naphthylmethyl	Me	—	789	9.648	315	–	–	–	–	1
B_9	2-Naphthylmethyl	Me	—	829	9.631	346	–	–	–	–	12
C_1	$SCH(CH_3)CH_2CH_3$	—	—	1898	13.046	535	–	–	±	–	1
C_2	Cl	—	—	1256	11.114	457	–	±	–	–	1
C_3	H	—	—	1144	10.704	442	–	–	–	–	1
C_4	OCH_3	—	—	1391	11.652	474		±	–	–	1
C_5	NH_2	—	—	1256	11.114	457	–	±	–	–	1
C_6	NH–NH–CS–NH_2	—	—	1920	13.008	537	–	–	±	–	1
D_1	S	H	Cyclohexyl	1256	11.114	457	–	±	–	–	1

Table 1 (*continued*)

Compd No.	R	R_1	X	W	χ	ξ^c	Anti-HIV activity				SI
							Predicted			Reported	
							W	χ	ξ^c		
D_2	O	CH_3	Cyclohexyl	1373	11.542	474	±	±	–	–	1
D_3	O	H	sec-Butyl	986	9.952	368	–	–	–	+	100
D_4	O	H	Cyclopentyl	1101	10.614	409	–	–	–	+	500
D_5	O	H	Cyclohexyl	1256	11.114	457	–	±	–	+	500

+, Active compound.
–, Inactive compound.
±, Compound in the transitional range where activity could not be specifically assigned.
SI, Selectivity index.

Table 2. Proposed models for the prediction of anti-HIV activity

Model index	Nature of range in the proposed model	Index value	Number of analogues falling in the range		Percent accuracy of prediction	Average EC_{50} (μM)	Overall accuracy of prediction	Average SI	Percentage of analogues having SI value ⩾20
			Total	Correct					
W	Lower inactive	<1258	43	38	88.4	159.1		35.2	9.3
	Transitional	1258–1391	8	N.A.	N.A.	68.4	88.13	156.5	25
	Active	1396–1638	9	8	88.9	4.6		64.8	88.9
	Upper inactive	>1638	7	6	85.7	118.2		19.2	28.6
χ	Lower inactive	<11.097	39	35	89.7	166.5		166.5	7.7
	Transitional	11.097–11.652	14	N.A.	N.A.	64.4	88.7	64.4	35.7
	Active	11.69–12.276	7	6	85.7	5.1		71.7	85.7
	Upper inactive	>12.276	7	6	85.7	118.2		19.2	28.6
ξ^c	Lower inactive	<494	51	43	84.3	142.1		54.9	13.7
	Active	494–519	5	5	100	3.4	86.4	59.0	80
	Transitional	535–596	8	N.A.	N.A.	54.7		44.8	50
	Upper inactive	>596	3	3	100	145.9		9.1	33.3

N.A., not applicable.

EC_{50} value was found to be 3.42 μM, indicating the presence of highly active compound in the active range.

- The average SI value was found to be 59, indicating the presence of non-toxic compounds in the active range. Four out of five analogues in the active range had a SI value more than 20.
- Transitional range had an *eccentric connectivity index* value of 535–596. The average EC_{50} value was found to be 54.7 μM for the analogues in the transitional range. The average SI value was found to be 44.8.

5. Discussion

Investigations reveal significant correlation between the topological indices used in the present study and anti-HIV activity of dihydro (alkylthio) (naphthylmethyl) oxopyrimidines. The overall degree of prediction was found to be 88% in case of *Wiener's index*, ~89% in case of *molecular connectivity index* and 86% in case of *eccentric connectivity index*. The analogues in the active range possess high anti-HIV activity and low toxicity. The analogues in the transitional range have a high value of selectivity index, but possess lower anti-HIV activity. Careful examination of the structure of the compounds in the active range indicates that the substitution at position-6 of the pyrimidine ring is most critical for the activity. A naphthylmethyl group at position-6 is essential for anti-HIV activity. Analogues with a smaller or bulkier substituent at position-6 are devoid of anti-HIV activity. Compounds with phenyl, phenylethyl, phenoxymethyl, (phenylthio)methyl or methyl group at position-6 are inactive as well as toxic. Possibly a naphthylmethyl group at position-6 can be better accommodated by the enzyme during drug–enzyme interaction. Further, the absence of bulkier group at position-2 is also correlated with the antiviral activity. Compounds, in which substituent at position-2 are absent lie outside the active range and are devoid of anti-HIV activity.

6. Conclusion

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

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