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Topological models for prediction of anti-HIV activity of acylthiocarbamates

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Abstract—Relationship of anti-HIV activity of acylthiocarbamates with distance based *Wiener's index*, adjacency based *first-order molecular connectivity index* and distance-cum-adjacency based *augmented eccentric connectivity index* was investigated. The values of all the three indices for each of the 61 compounds involved in the dataset were calculated using an in-house computer program. Resulting data was analyzed and suitable models were developed after identification of the active ranges. Subsequently, biological activity was assigned to each of the compounds involved in the dataset using these models which was then compared with the reported anti-HIV activity. Very high accuracy of prediction ranging from 95% to 98% was observed using these topological models.

1. Introduction

The discovery of the human immunodeficiency virus (HIV) as the causative agent of AIDS has led to enormous efforts to unravel the basic action of the virus at a molecular level. From this effort, a variety of targets for potential intervention of HIV multiplication have been identified.[1] Inhibition of reverse transcriptase (RT), the human immunodeficiency virus (HIV)-encoded polymerase which directs both RNA and DNA dependent DNA synthesis, has proven to be one of the most effective ways to block viral multiplication.[2,3] Inhibitors of reverse transcriptase are generally classified as nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). NRTIs are active against both HIV-1 and HIV-2 but unfortunately resistance development; limitations in efficacy and toxicity are some of their severe drawbacks.[4,5] NNRTIs, in general, are selective inhibitors of HIV-1 with no activity against HIV-2 or any other nucleic acid polymerase.[6] Examples of NNRTIs include TIBO compounds,[7] HEPT derivatives,[8] BHAP analogs,[9] 2-pyridinones,[10] and PETT compounds,[6] etc. 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.[11,12]

In the last decade, synthetic chemists have done tremendous research efforts for the development of newer anti-HIV agents. Structure-based design, spurred by the significant pitfalls of the traditional method and the rapid advances in molecular-structure determination and computational resources, has now been accepted as a rational approach for the generation of new pharmaceuticals. The successful implementation of quantitative structure–property/activity relationship (QSPR/QSAR) certainly decreases the number of compounds synthesized, by making it possible to select most promising compounds.[13] Nonempirical parameters of chemical structure derived from graph theoretic formalism are being used more frequently by many researchers in QSAR studies pertaining to molecular design, pharmaceutical drug-design, and environmental hazard assessment of chemicals. In chemistry, a graph represents the topology of a molecule in the sense that it depicts the pattern of connectedness of atoms in the molecule, being, at the same time, independent of such metric aspects of molecular structure as equilibrium distance between nuclei, bond angles, etc.[14] 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

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and adjacency matrix, which represent a molecular graph. Though numerous topological descriptors have been reported in the literature but only handful of them have been successfully employed for structure–activity relationship studies. Notable amongst these are Wiener's index,[15–17] Randic's connectivity index,[18] and eccentric connectivity index.[19]

In the present investigation, relationship of Wiener's index, first-order molecular connectivity index and augmented eccentric connectivity index with anti-HIV activity of a recently reported, novel series of potent, selective HIV-1 *N*-acylthiocarbamate (ATC) non-nucleoside reverse transcriptase inhibitors has been investigated and suitable models have been developed for prediction of anti-HIV activity. This series of compounds has been reported to be structurally related to phenylethylthiazolylthiourea (PETT) derivatives and have anti-HIV-1 activity coupled with low toxicity.[20]

1.1. Wiener's index

Wiener number or Wiener's index, W, is the first reported and used topological index in Chemistry. The Wiener's index is defined as the 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 the graph G and n is the maximum possible number of i and j.[21–23]

1.2. Molecular connectivity index

One of the pioneering topological indices, which is widely applicable to structure–activity studies, is molecular connectivity index which was proposed by Randic in 1975 and was referred to as branching index.[24] It was later expanded to broaden its applications and the chemical literature now uses the term molecular connectivity. Randic's branching index is now referred to as first-order or path-one molecular connectivity index, ${}^{1}\chi$. It is defined as the sum over all the edges (ij) as per the following:

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

where V_i and V_j are the degrees of adjacent vertices i and j and n is the number of vertices in the hydrogen suppressed molecular structure.[23–25]

1.3. Augmented eccentric connectivity index

This is an adjacency-cum-distance based index and is defined as the summation of the quotients of the product of adjacent vertex degrees and eccentricity of the concerned vertex, for all vertices in the hydrogen suppressed molecular graph. It is expressed as

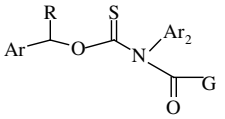
$${}^{A}\xi^{c} = \sum_{i=1}^{n}\left(\frac{M_i}{E_i}\right), \tag{3}$$

where, M_i is the product of degrees of all vertices (v_j), adjacent to vertex i, E_i is the eccentricity, and n is the number of vertices in graph G. For a molecular graph (G), v_1, v_2, …, v_n are vertices and the number of first neighbors of a vertex v_i is the degree of this vertex. The distance d (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. The, eccentricity E_i of vertex v_i, in graph G is the length of shortest path from v_i to vertex v_j that is farthest from v_i ($E_i = \max d(v_i, v_j); j|G$).[27]

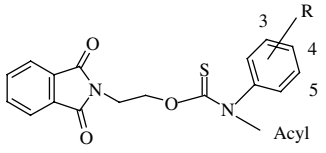
Augmented eccentric connectivity index is a novel modification of the eccentric connectivity index, with augmented discriminating power. The new index offers the advantages of exceptionally high discriminating power and absence of degeneracy up to five vertices.[27]

1.4. Model development and analysis

A dataset comprising of 61, recently reported,[20] acylthiocarbamates was used for the present investigations. The basic structure of the compounds has been presented in Figure 1. The dataset comprises compounds having anti-HIV activity in MT-4 cells using trovirdine as reference. The activity of the compounds has been reported in terms of EC_{50} (μM).[20] EC_{50} (μM) has been defined as the compound concentration [μM] to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity, as determined by the MTT method. The values of all the three indices, viz., Wiener's index, first-order molecular connectivity index and augmented eccentric connectivity index were computed using in-house computer program. Resulting data was analyzed and suitable models were developed after identification of the active ranges by maximization of moving average with respect to the active analogues.[26–31] Subsequently, each analogue was assigned biological activity, which was then compared with the reported anti-HIV activity. The compounds having EC_{50} (μM) value less than or equal to 0.5 were considered to be active while those having this value higher than 0.5 were considered to be inactive for the purpose of this study. The percent degree of prediction for each range was calculated from the ratio of number of compounds for which activity



Basic structure I (Compounds **1-33**)



Basic structure II (Compounds **34-61**)

Figure 1. Basic structures of acylthiocarbamates.

was predicted correctly to that of total number of compounds present in the respective active or inactive 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 degree of classification was calculated from the ratio of number of compounds in both active and inactive ranges to total number of compounds in the dataset.

The results have been compiled in Tables 2 and 3.

2. Results

In this study three topological descriptors, viz. Wiener's index, first-order molecular connectivity index and augmented eccentric connectivity index were employed for investigating relationship between anti-HIV-1 activity and structure of 61 acylthiocarbamates. Retrofit analysis of the data in Tables 1 and 2 reveals the following information with respect to models based upon Wiener's index, first-order molecular connectivity index and augmented eccentric connectivity index.

2.1. Model based upon Wiener's index

- Biological activity was assigned to 44 out of 61 compounds. Out of these biological activities of 43 (97.72%) compounds were predicted correctly with respect to anti-HIV-1 activity.
- The compounds having Wiener's index values less than 2805 were classified as inactive. All the 34 compounds in the inactive range had EC_{50} (μM) value more than 0.5 and were considered as inactive. The correctly predicted compounds in the inactive range had an average EC_{50} (μM) value of 26.55.
- The active range had Wiener's index values from 3080 to 3382. Nine out of 10 compounds in the active range were predicted correctly. The correctly predicted compounds in the active range had an average EC_{50} (μM) value of 0.10.
- Active range was ideally bracketed by two transitional ranges. The lower transitional range had Wiener's index values between 2805 and 3079. The average EC_{50} (μM) value in this range was 4.09. The upper transitional range had Wiener's index value greater than 3382. The average EC_{50} (μM) value in this range was 8.02.
- For estimation of EC_{50} (μM), the following equation was developed:

$$EC_{50}\ (\mu M) = -0.0016\ (W) + 5.42.$$

2.2. Model based upon first-order molecular connectivity index

- Biological activity was assigned to 34 out of 61 compounds. Out of these biological activities of 33 (97.06%) compounds were predicted correctly with respect to anti-HIV-1 activity.
- The compounds having molecular connectivity index values equal to or less than 14.952 were classified as inactive. All the 29 compounds in the inactive range had EC_{50} (μM) value more than 0.5 and were considered as inactive. The compounds in the inactive range had an average EC_{50} (μM) value of 29.52.
- The active range had molecular connectivity index values from 15.863 to 15.880. Six out of seven compounds in the active range were predicted correctly. The correctly predicted compounds in the active range had average EC_{50} (μM) of 0.07.
- Active range was ideally bracketed by two transitional ranges. The lower transitional range had molecular connectivity index values from 14.953 to 15.862. The average EC_{50} (μM) value in this range was 4.77. The upper transitional range had molecular connectivity index value greater than 15.880. The average EC_{50} (μM) value in this range was 8.02.
- For estimation of EC_{50} (μM), the following equation was developed:

$$EC_{50}\ (\mu M) = 3.9331\ ({}^1\chi)^2 - 107.89({}^1\chi) + 740.15.$$

2.3. Model based upon augmented eccentric connectivity index

- Biological activity was assigned to all the 61 compounds. Out of these biological activities of 58 (95.08%) compounds were predicted correctly with respect to anti-HIV-1 activity.
- Two inactive ranges were identified. The lower inactive range had augmented eccentric connectivity index values of less than 21.768 and all the 33 compounds in this range had EC_{50} (μM) values more than 0.5 and were considered as inactive. The upper inactive range had augmented eccentric connectivity index values greater than 23.123. Ten out of 11 compounds in this range were predicted correctly. The overall predictability in the both the inactive ranges was 97.72%. The correctly predicted compounds in both the inactive ranges had average EC_{50} (μM) of 17.93.
- The active range had augmented eccentric connectivity index values from 21.768 to 23.123. Fifteen out of 17 compounds in the active range were predicted correctly. The correctly predicted compounds in the active range had average EC_{50} (μM) of 0.14.

3. Discussion and conclusions

For a long time, chemists have primarily relied upon visual perception in order to relate various aspects of constitutional graphs (structure) to observable chemical phenomena. But a clear and quantitative understanding of the structural basis of properties of molecules necessitates the use of precise mathematical techniques.[14] In structure–activity relationship studies, molecular topology quantifies chemical structures by translation of chemical structure into characteristic numerical

Table 1. Relationship of Wiener's index (W), first-order molecular connectivity index ($^1\chi$) and augmented eccentric connectivity index ($^A\xi^c$) with anti-HIV-1 activity of acylthiocarbamates

No.	Compounds having basic structure I				W	$^1\chi$	$^A\xi^c$	Anti-HIV-1 activity			
	Functional groups							Assigned			Reported
	Ar	R	Ar_2	AR_1–CO				W	$^1\chi$	$^A\xi^c$	
1	Phenyl	H	C_6H_5	2-Furoyl	1370	11.754	19.356	–	–	–	–
2	2-Furyl	H	C_6H_5	Benzoyl	1354	11.754	20.513	–	–	–	–
3	Benzyl	H	C_6H_5	*trans*-Cinnamoyl	2277	13.737	16.632	–	–	–	–
4	Benzyl	H	C_6H_5	Benzoyl	1770	12.754	17.655	–	–	–	–
5	Benzyl	H	C_6H_5	4-Chlorobenzoyl	1970	13.148	17.737	–	–	–	–
6	Benzyl	H	C_6H_5	2-Furoyl	1593	12.254	17.930	–	–	–	–
7	Phenoxymethyl	H	C_6H_{11}	Benzoyl	2034	13.254	16.543	–	–	–	–
8	Phenoxymethyl	H	C_6H_5	Phenoxyacetyl	2580	14.237	15.709	–	–	–	–
9	Phenoxymethyl	H	C_6H_5	*trans*-Cinnamoyl	2580	14.237	15.709	–	–	–	–
10	Phenoxymethyl	H	C_6H_5	Benzoyl	2034	13.254	16.543	–	–	–	–
11	Phenoxymethyl	H	C_6H_5	4-Toluoyl	2251	13.648	16.589	–	–	–	–
12	Phenoxymethyl	H	C_6H_5	4-Chlorobenzoyl	2251	13.648	16.589	–	–	–	–
13	Phenoxymethyl	H	C_6H_5	2-Acetoxybenzoyl	2878	15.059	18.516	±	±	–	–
14	Phenoxymethyl	H	C_6H_5	2,4-Dichlorobenzoyl	2430	14.096	16.596	–	–	–	–
15	Phenoxymethyl	H	C_6H_5	3,5-Dichlorobenzoyl	2430	14.042	17.829	–	–	–	–
16	Phenoxymethyl	H	C_6H_5	4-Chloro-3-nitrobenzoyl	2908	14.969	18.519	±	±	–	–
17	Phenoxymethyl	H	C_6H_5	3,4,5-Trimethoxybenzoyl	3388	16.083	19.451	–	±	–	–
18	Phenoxymethyl	H	C_6H_5	2-Furoyl	1841	12.754	16.688	–	–	–	–
19	Phenoxymethyl	H	C_6H_5	2-Thenoyl	1841	12.754	16.688	–	–	–	–
20	Phenoxymethyl	H	4-F-C_6H_5	Benzoyl	2240	13.648	17.091	–	–	–	–
21	Phenoxymethyl	CH_3	C_6H_5	Benzoyl	2752	14.631	16.497	–	–	–	–
22	Phenoxymethyl	CH_3	C_6H_5	Benzoyl	2181	13.648	17.527	–	–	–	–
23	Phenoxymethyl	CH_3	C_6H_5	Benzoyl	2856	14.952	18.579	±	–	–	–
24	Phenoxymethyl	CH_3	C_6H_5	Benzoyl	3023	15.631	20.702	±	±	–	–
25	Phenoxymethyl	CH_3	C_6H_5	Benzoyl	1979	13.148	17.742	–	–	–	–
26	Phenoxymethyl	CH_3	C_6H_5	2-Thenoyl	1979	13.148	17.742	–	–	–	–
27	Phenoxymethyl	CH_3	C_6H_5	2-Thenoyl	2163	13.542	18.399	–	–	–	–
28	Phenoxymethyl	CH_3	C_6H_5	2-Thenoyl	2184	13.542	17.789	–	–	–	–
29	Phenoxymethyl	CH_3	C_6H_5	2-Thenoyl	2652	14.552	18.233	–	–	–	–
30	Phenylthiomethyl	H	C_6H_5	Benzoyl	2034	13.254	16.543	–	–	–	–
31	Phenoxymethyl	CH_3	C_6H_5	*n*-Propoxycarbonyl	1850	12.613	15.411	–	–	–	–
32	Phenoxymethyl	CH_3	C_6H_5	*n*-Butoxycarbonyl	2072	13.113	15.127	–	–	–	–
33	Phenoxymethyl	CH_3	C_6H_5	Phenoxycarbonyl	2452	14.131	16.910	–	–	–	–

No.	Compounds having basic structure II		W	$^1\chi$	ξ^A	Anti-HIV-1 activity			
	Functional groups					Assigned			Reported
	R	Acyl				W	$^1\chi$	ξ^A	
34	H	Benzoyl	3825	15.075	21.968	±	±	+	+
35	2-CH_3	2-Thenoyl	2780	14.986	23.656	–	±	–	–
36	2-C_2H_5	2-Thenoyl	3008	15.524	24.356	±	±	–	–
37	2-Cl	2-Thenoyl	2780	14.986	23.656	–	±	–	–
38	2-OCH_3	2-Thenoyl	3008	15.524	24.356	±	±	–	–
39	3-CH_3	2-Thenoyl	2804	14.969	23.297	–	–	–	–
40	3-CF_3	2-Thenoyl	3566	16.181	24.197	–	–	–	–
41	3-$COCH_3$	2-Thenoyl	3310	15.880	23.435	+	+	–	–
42	3-F	2-Thenoyl	2804	14.969	23.297	–	±	–	–
43	3-Cl	2-Thenoyl	2804	14.969	23.297	–	±	–	–
44	3-Br	2-Thenoyl	2804	14.969	23.297	–	±	–	–
45	3-NO_2	2-Thenoyl	3310	15.880	23.435	+	+	–	+
46	3-OCH_3	2-Thenoyl	3056	15.507	22.816	±	±	–	–
47	4-CH_3	2-Thenoyl	2828	14.969	22.230	±	±	+	+
48	4-C_2H_5	2-Furoyl	3104	15.507	21.768	+	±	+	+
49	4-F	2-Thenoyl	2828	14.969	22.230	±	±	+	+
50	4-Cl	Benzoyl	3080	15.469	22.516	+	±	+	+
51	4-Cl	4-Chlorobenzoyl	3361	15.863	22.121	+	+	+	+
52	4-Cl	2-Furoyl	2828	14.969	22.230	±	±	+	+
53	4-Cl	2-Thenoyl	2828	14.969	22.230	±	±	+	+
54	4-Cl	2-Chloronicotinoyl	3335	15.863	23.123	+	+	+	+
55	4-Cl	6-Chloronicotinoyl	3335	15.863	23.123	+	+	+	+
56	4-Br	Benzoyl	3080	15.469	22.516	+	±	+	+
57	4-I	2-Thenoyl	2828	14.969	22.230	±	±	+	+

Table 1 (*continued*)

No.	Compounds having basic structure II		W	$^1\chi$	ξ^A	Anti-HIV-1 activity			
	Functional groups					Assigned			Reported
	R	Acyl				W	$^1\chi$	ξ^A	
58	4-N(C_2H_5)$_2$	2-Thenoyl	4008	16.956	22.480	–	–	+	–
59	4-NO_2	2-Furoyl	3382	15.880	22.343	+	+	+	+
60	4-NO_2	2-Thenoyl	3382	15.880	22.343	+	+	+	+
61	4-OC_2H_5	6-Chloronicotinoyl	3965	14.901	22.245	–	–	+	+

Note: (+) active compound, (–) inactive compound and (±) compound in transitional range.

Table 2. Proposed models for prediction of anti-HIV 1 activity of acylthiocarbamates

Model index	Nature of range in proposed model	Index value	Number of compounds in each range		Percent accuracy	Average EC_{50} (μM)[b] of compounds in each range	
			Total	Correctly predicted		Total	Correctly predicted
W	Inactive	<2805	34	34	100.0	26.55	26.55
	Lower transitional	2805–3079	13	NA[a]	NA	4.09	NA
	Active	3080–3382	10	9	90.0	0.69	0.10
	Upper transitional	>3382	4	NA	NA	8.02	NA
$^1\chi$	Inactive	⩽14.952	29	29	100.0	29.52	29.52
	Lower transitional	14.952–15.862	21	NA	NA	4.77	NA
	Active	15.863–15.880	7	6	85.7	0.92	0.07
	Upper transitional	>15.880	4	NA	NA	8.02	NA
$^A\xi^c$	Lower Inactive	<21.768	33	33	100.0	26.93	26.93
	Active	21.768–23.123	17	15	88.2	0.96	0.13
	Upper Inactive	>23.123	11	10	90.9	8.14	8.92

[a] NA: not applicable.
[b] EC_{50}: effective concentration (μM).

descriptors. Since 3-D structure of a compound depends on the connectivity of its constituent atoms, the numerical topological descriptors derived from information based on connectivity can reveal structural or sub-structural information of a molecule. Topological descriptors developed for predicting physicochemical properties and biological activities, of chemical substances, can be used for drug design.[26] The present study is one such attempt to develop understanding and relationship about the structural properties and anti-HIV activity of recently introduced acylthiocarbamates. This group of compounds has been reported to share some structural features of PETT derivatives, show anti-HIV-1 activity and have low cytotoxicity. In the dataset enzyme assays against virion-associated RT (vRT) were also reportedly performed with the three most potent compounds and the activity was compared with Nevirapine and Troviridine. The encouraging results, clearly indicates that this group of compounds is a promising series to work upon.

The three topological indices used in this study have yielded excellent models for prediction of activity of this series of compounds especially the model based upon augmented eccentric connectivity index. Comparison of the models, Table 3, reveals that though the accuracy of prediction using Wiener's index and molecular connectivity index is slightly higher, but the classification is much lower when compared to the model based upon augmented eccentric connectivity index, where the classification is 100%. This is indicative of the fact that this model will be applicable for prediction of activity of any new compound proposed to be synthesized in this series. In the models based upon Wiener's index and first-order molecular connectivity index, the active range was ideally bracketed by two transitional ranges, which represents gradual transition of activity over the index values and that there is no overlapping between the active and inactive ranges. The three indices of diverse nature were utilized so as to provide structural information on three different principles. Wiener's index is based upon inter-atomic distances, molecular connectivity index is based upon adjacency or connectivity of atoms with in a molecule, and the third augmented eccentric connectivity index is based upon the combination of both adjacency as well as inter-atomic distance.

In-depth analysis of the structure of compounds in the active range reveals the following features of structure–activity relationship.

- Activity lies only with the *O*-2-(phthalimidoethyl) acylthiocarbamates (Basic structure II). All compounds (**1**–**33**, Basic structure I) having other groups are inactive.

Table 3. Intermodel comparison

Model index	Percent classification	Accuracy of prediction
W	72.13	97.72
$^1\chi$	55.73	97.06
$^A\xi^c$	100	95.08

- Presence of a halogen or a nitro group at position 4 of R (*N*-aryl group) is important for activity. Amongst the halogens, chloride is the most suitable. Compounds having halogen or nitro group at other positions (e.g., compounds **37**, **43** and **45**) are inactive. Compounds having methyl or ethyl group or no substitution at this position (e.g., compounds **47**, **48** and **34**) are active but are relatively less potent.
- In general five member compounds are more suitable as acyl group (Basic structure II), although compounds having six-member ring, with or without heteroatom, are also active. Amongst five member heterocyclic rings, activity is better with furfuryl group as in compounds **52**, **53**, **59** and **60**.

Aforementioned topological models possess vast potential for providing lead structures for development of potent anti-HIV agents.

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