Structure-Activity Study on Antiviral 5-Vinylpyrimidine Nucleoside Analogs Using Wiener's Topological Index

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The relationship between Wiener's topological index and the antiviral activity of a series of 5-vinylpyrimidine nucleoside analogs has been investigated. Values for more than 100 compounds were computed, and an active range was identified. The predicted activity of each compound was compared with reported antiviral activity against herpes simplex virus type I. Due to significant correlation between antiviral activity and Wiener's topological index, it was possible to predict antiviral activity with an accuracy of ~83%.

INTRODUCTION

The interest in the influence of molecular topology on molecular properties has grown remarkably during the past few years. The objective of all such studies is to explore the role of connectedness of atoms in the expression of biological activities of molecules.[1] Thus, molecular structures are translated into characteristic numerical descriptors known as topological indices, which may then be used in the development of structure–activity relationship (SAR) studies.[2] The use of topological indices in SAR seems to play an important role in situations where the biological activity is determined predominantly by topological architecture of molecular structure, i.e. where simple connectivity among neighboring atoms, without considering the chemical nature of atoms or the nature of chemical bonding, may be the major determinant of biological activity of a molecule.[1] Such an approach[3-6] was initiated by H. Wiener in 1947 with the use of indices based on topological distances. The path number developed by Wiener, now known as Wiener's topological index, is equal to one-half the sum of elements of the distance matrix $\mathbf{D}(G)$.

$$W(G) = {}^1/_2 \sum_{ij} D(G)$$

where $D(G)$ represents off-diagonal elements of $\mathbf{D}(G)$. The smaller the Wiener's number, the greater the compactness of molecules.[2]

Many indices have been devised.[2,7-9] From them, Randic's molecular connectivity index,[10,11] Hosoya's index,[12,13] and Balaban's index J[14-16] appear to be the most useful. Bonchev and Trinajstic devised information theoretical indices[17-19] and proposed a superindex[20] consisting of a sum of 10 different topological indices. Some other indices based on adjacency and distance matrix include the Zagreb group index,[21,22] the comparability index,[23] Platt's number,[24,25] Gordon–Scantleburry's index,[26] Altenburg's polynomial,[27] Smolenskii's additivity index,[28] and the centric index.[8] Various topological indices have different correlating abilities with physical, chemical, or biological properties of molecules.[29]

In the present studies, an attempt has been made to correlate Wiener's index with the antiviral activity of 5-vinylpyrimidine nucleoside analogs. Antiviral chemotherapy is at the same stage today as antibacterial chemotherapy was half a century ago.[30] Although there are many compounds that have potent antiviral activity in cell cultures, only 10 synthetic compounds have been approved by FDA for clinical use.[31] None of these drugs, however, are without toxicity, and hence there is a strong need for improved drugs not only to improve efficiency but also to circumvent these problems of toxicity. There is also a need to find an effective therapy for viral infections for which we do not at present have clinically useful drugs, an important infection being aquired immune deficiency syndrome (AIDS).[32-34] The search for new antiviral drugs has been boosted by the advent of AIDS and identification of HIV as the etiological agent.[35]

Consequently, the need for treatment of viral infection is enormous, as currently available drugs barely scratch the surface, but the development of antiviral compounds has been hampered by a number of problems,[33] the major ones being the following:

(a) Selectivity, or inhibition of virus infection and reproduction without causing adverse effects to host cells; that is, the drug must be designed rationally on exploitable biochemical differences that exist between virus-specific processes and cellular biosynthetic processes.

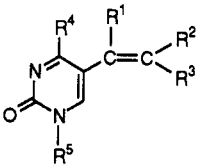

Figure 1. 5-Vinyl-2-pyrimidones.

Table 1. List of R^5 Substituents

base number	name
I	β-2′-deoxyribosyl
II	α-2′-deoxyribosyl
III	2′-fluoroarabinosyl
IV	arabinosyl
V	(2-hydroxyethoxy)methyl
VI	5′-chloro-2′,5′-dideoxyribosyl
VII	5′-bromo-2′,5′-dideoxyribosyl
VIII	5′-iodo-2′,5′-dideoxyribosyl
IX	5′-azido-2′,5′-dideoxyribosyl
X	5′-amino-2′,5′-dideoxyribosyl
XI	2′-deoxyxylosyl
XII	3′-chloro-2′,3′-dideoxyribosyl
XIII	3′-azido-2′,3′-dideoxyribosyl
XIV	3′-amino-2′,3′-dideoxyribosyl
XV	3′-azido-2′,3′-dideoxyribosyl
XVI	3′-amino-2′,3′-dideoxyxylosyl
XVII	4-hydroxybutyl

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Table 2. Relationship between Wiener's Topological Index and Antiviral Activity of 5-Vinylpyrimidine Nucleoside Analogs and Congeners (Boxes Indicate the Substituents Replacing the 5-Vinyl Group)

compd no.	R^1	R^2	R^3	R^4	R^5	Wiener's index	antiviral activity: predicted	antiviral activity: reported	references
1	5-acetyl			OH	H	150	–[a]	–	45, 47
2	5-ethynyl			OH	H	116	–	–	45, 47
3	5-ethynyl			NH_2	H	116	–	–	46, 47
4	H	H	H	OH	H	116	–	–	47
5	Cl	H	H	OH	H	150	–	–	47
6	H	Br	H	OH	H	158	–	–	47
7	5-acetyl			OH	I	683	+[b]	+	47
8	5-ethynyl			OH	I	593	+	+	38, 48, 49
9	5-ethynyl			OH	IV	668	+	+	48
10	5-ethynyl			NH_2	I	593	+	+	50
11	H	H	H	OH	I	593	+	+	38, 49, 51
12	H	H	H	NH_2	I	593	+	+	51
13	H	H	H	OH	III	668	+	+	52
14	H	H	H	OH	IV	668	+	+	53–55
15	H	Br	H	OH	I	699	+	+	38, 49, 56
16	H	H	Br	OH	I	699	+	+	57
17	H	I	H	OH	I	699	+	+	38, 49, 56
18	H	Cl	H	OH	I	699	+	+	56
19	H	Br	H	NH_2	I	699	+	+	50
20	H	I	H	NH_2	I	699	+	+	50
21	H	H	F	OH	I	699	+	–	58
22	H	F	H	OH	I	699	+	+	58
23	H	Br	H	OH	IV	782	+	+	53, 55, 59, 60, 81
24	H	Br	H	OH	IV	782	+	+	52
25	H	I	H	OH	III	782	+	+	52
26	H	Cl	H	OH	III	782	+	+	52
27	H	Cl	H	OH	IV	782	+	+	53, 55, 81
28	H	Br	H	OH	V	478	–	–	47, 61
29	Cl	H	H	OH	I	683	+	–	38
30	Cl	Br	H	OH	I	802	+	+	62
31	H	$COOCH_3$	H	OH	I	1096	–	+	63
32	H	Br	H	OH	VI	699	+	+	64
33	H	Br	H	OH	VII	699	+	+	64
34	H	Br	H	OH	VIII	699	+	+	64, 56
35	H	Br	H	OH	IX	963	±[c]	–	64
36	H	Br	H	OH	X	782	+	+	64
37	H	Br	H	OH	XI	782	+	–	64
38	H	Br	H	OH	XII	782	+	–	64
39	H	Br	H	OH	XIII	935	±	+	64, 56
40	H	Br	H	OH	XIV	782	+	+	64, 65
41	H	Br	H	OH	XV	935	●	+	64
42	H	Br	H	OH	XVI	782	+	+	64
43	H	CN	H	OH	I	824	+	+	63, 66
44	H	CN	H	OH	IV	916	±	–	38
45	H	CH_3	H	OH	I	782	+	+	67–69
46	H	C_2H_5	H	OH	I	824	+	+	69
47	H	$CH{=}CH_2$	H	OH	I	824	+	+	70
48	H	SCH_3	H	OH	I	824	+	+	63
49	H	H	CH_3	OH	I	782	+	+	63
50	H	CH_3	H	SH	I	782	+	+	63
51	H	CH_3	H	NH_2	I	782	+	+	63
52	H	H	CH_3	NH_2	I	782	+	+	63
53	H	C_3H_7	H	OH	I	967	●	–	63
54	H	C_4H_9	H	OH	I	1133	–	–	63
55	H	$C(CH_3)_3$	H	OH	I	1078	–	+	63
56	5-allyl			OH	I	782	+	+	69, 71
57	5-(2-chloroallyl)			OH	I	807	+	+	63
58	5-(2-butenyl)			OH	I	824	+	+	69
59	5-(but-3-en-1-ynyl)			OH	I	824	+	+	47
60	5-allylmercapto			OH	I	824	+	+	72
61	5-allyloxy			OH	I	824	+	+	73
62	H	CF_3	H	OH	I	1078	–	+	74
63	H	$C_2H_4CH_2Cl$	H	OH	I	1133	–	+	75
64	H	$C_2H_4CH_2CN$	H	OH	I	1322	–	+	75
65	H	C_8H_{17}	H	OH	I	2028	–	+	75
66	H	$CH{=}CHCOOCH_3$	H	OH	I	1486	–	–	63
67	H	$C_2H_4C{=}CH$	H	OH	I	1133	–	+	75
68	H	*p*-methoxyphenyl	H	OH	I	1828	–	–	75
69	H	OC_2H_5	H	OH	I	967	±	+	58, 75
70	H	C_2H_4COOH	H	OH	I	1298	–	–	75
71	H	C_5H_{11}	H	OH	I	1531	–	–	75
72	H	$C_8H_{16}COOCH_3$	H	OH	I	3278	–	–	75
73	H	$C(CH_3){=}CH_2$	H	OH	I	864	+	–	75

Table 2 (Continued)

compd no.	R^1	R^2	R^3	R^4	R^5	Wiener's index	antiviral activity: predicted	antiviral activity: reported	references
74	H	1-chloro-2,2,3,3-tetramethylcyclopropyl	H	OH	I	1732	–	–	75
75	H	1-hydroxycyclopentenyl	H	OH	I	1398	–	+	75
76	H	H	C_4H_9	OH	I	1132	–	–	47
77	H	CH_3	H	OH	IV	782	+	+	76
78	H	C_2H_5	H	OH	IV	915	±	+	76
79	H	CH_3	CH_3	OH	I	807	+	+	63
80	CH_3	CH_3	H	OH	I	802	+	+	63
81	CH_3	H	CH_3	OH	I	802	+	–	63
82	CH_3	$COOCH_3$	H	OH	I	1203	–	–	63
83	H	$COOCH_3$	CH_3	OH	I	1219	–	–	63
84	H	Br	CH_3	OH	I	807	+	+	63
85	H	CH_3	Br	OH	I	807	+	+	63
86	CH_3	Br	H	OH	I	802	+	+	63
87	H	Br	Br	OH	I	807	+	+	63
88	H	COOH	F	OH	I	1065	–	–	58
89	CH_3	Cl	H	OH	I	802	+	–	63
90	C_2H_5	C_2H_5	H	OH	I	1039	–	–	75
91	F	Cl	Cl	OH	I	913	±	+	77
92	F	Cl	Cl	OH	II	913	±	–	77
93	F	F	Cl	OH	I	913	±	+	77
94	F	Cl	F	OH	I	913	±	–	77
95	F	F	CF_3	OH	I	1307	–	–	77
96	F	CF_3	F	OH	I	1307	–	–	77
97	H	phenyl	H	OH	I	1415	–	+	78
98	H	*m*-nitrophenyl	H	OH	I	1813	–	–	78
99	H	*m*-azidophenyl	H	OH	I	2012	–	–	78
100	H	H	H	OH	XVII	393	–	–	80
101	H	Br	H	OH	XVII	478	–	–	80
102	H	Br	Br	OH	XVII	563	±	+	80
103	H	H	H	OH	V	478	–	–	80
104	H	Br	Br	OH	V	563	±	–	80
105	H	I	C_4H_3	OH	V	782	+	+	80
106	5-phenyl			OH	I	1040	–	–	47
107	5-(2-phenylethyl)			OH	I	1415	–	+	78
108	5-phenylethynyl			OH	I	1415	–	–	65
109	5-(3-nitrophenyl)			OH	I	1440	–	–	47
110	5-anilino			OH	I	1040	–	+	79
111	$CH(OH)CH_2Br$			OH	I	802	+	+	82
112	$CH(OH)CH_2Cl$			OH	I	802	+	+	82
113	$CH(OCH_3)CH_2Br$			OH	I	915	±	+	82
114	$CH(OCH_3)CH_2Cl$			OH	I	915	±	+	82
115	$CH(OH)CH(Br)COOCH_3$			OH	I	1607	–	+	82
116	$CH(OH)CH_2I$			OH	I	802	+	+	82
117	CH(Br)CH(OH)I			OH	I	913	±	+	82
118	CH(OH)CH(OH)I			OH	I	913	±	+	82

[a] Negative antiviral activity. [b] Positive antiviral activity. [c] Transitional range where activity could not be specifically assigned.

(b) Development of drug resistance resulting from selection and overgrowth of viral populations, e.g. in treatment of HSV infection with acyclovir.[36]

(c) Latency, perhaps the most difficult problem of all; presently no solution seems to be in sight.

(d) Drug delivery and drug metabolism, which are being approached with the use of liposomes and prodrugs, respectively.

Despite the above-mentioned limitations, antiviral chemotherapy has witnessed rapid progress, especially in the late 1980s and early 1990s. Recent trends in antiviral drug design have been focused on the development of derivatives of existing drugs as well as on the synthesis of entirely new antiviral agents. The first approach is aimed at either increasing potency, decreasing the toxicity, widening the antiviral spectrum, or improving pharmacokinetic profiles of currently available drugs.[37] This is the approach where the concept of the structure–function relationship can be successfully exploited. To assist in the identification and development of more effective antiviral agents, the SAR of 5-vinylpyrimidine nucleoside analogs has been studied in the present investigations. These compounds have been shown to have selective and potent antiviral properties.[38] The compounds included in the study have been reportedly evaluated against herpes simplex virus (HSV) type I in cell culture.

METHODOLOGY

Antiviral agents have been extensively reviewed.[31-35,37,39-43] A set of active and inactive analogs based on 5-vinylpyrimidine as depicted in Figure 1 was selected. Various sugar substituents of R^5 are listed in Table 1. As for R^4 substitutions, compounds with R^4 = OH will exhibit tautomerism with NHCO instead of the N=C(OH) group, as indicated by the formula. The Wiener's index value for each compound was computed from the hydrogen-suppressed molecular structure of the compounds. The index values so obtained were classified into active, transitional, and inactive ranges. These ranges were then employed to predict activity of molecules on the basis of computed Wiener's index values. For 5-vinylpyrimidone nucleoside analogs, Wiener's index values of 576–900 were selected as an active range. Compounds with values less than 500 and greater than 975 have been predicted to be

Table 3. Relative Distribution of Test Compounds in Various Ranges of Wiener's Topological Index Values

S no.	ranges of Wiener's index value	nature of range	total number of compounds falling within the range	compounds predicted correctly	accuracy of prediction
1	500 or less	inactive	10	10	100%
2	501–575	lower transitional range	2	not applicable	not applicable
3	576–900	active	60	52	86.66%
4	901–975	upper transitional range	15	not applicable	not applicable
5	976 or more	inactive	31	19	61.29%

inactive against HSV-I infection. The intermediate ranges, i.e. 501–575 and 901–975, were selected as transitional or borderline ranges where antiviral activity could not be specifically assigned on the basis of their Wiener's index values.

RESULTS AND DISCUSSION

A retrofit study of Table 2 shows that a total of 81 out of 101 compounds were classified correctly within active and inactive ranges. The relative distribution of test compounds falling under various ranges of Wiener's topological index along with predicted and reported activities has been compiled in Table 3.

Wiener's index was found to be a promising topological descriptor as the results obtained in the above work showed 82.65% accuracy in prediction. However, when the upper transitional range of Wiener's index values was modified to 900–1100, the correlation between the Wiener's index value and antiviral activity resulted in an enhancement of prediction accuracy to 85.22%.

Some of the mispredictions in the above work may be due to high degeneracy for Wiener's index values, probably due to the following: (i) Wiener's index gives the same value for both α and β anomers, while as a general rule, all α anomers are inactive or have relatively weak activity, i.e. compounds 91 and 92.

(ii) *E* and *Z* isomers give the same value for Wiener's index, while C-5 compounds with only *E* stereochemistry are found to be more active, i.e. compounds 21, 22, 51, 52, 80, and 81.

However despite these shortcomings, Wiener's index was found to have a highly significant correlating ability with biological properties of 5-vinylpyrimidines. The initial results obtained from this study show considerable promise regarding the usefulness of topological indices in the SAR of antiviral agents. Further studies on the SAR of antiviral agents with the main emphasis on anti-AIDS activity are under progress and will be communicated shortly.

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