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A Quantitative Structure–Activity Relationship Study on Some HIV-1 Protease Inhibitors Using Molecular Connectivity Index

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Abstract—A quantitative structure–activity relationship (QSAR) study has been made on two different series of tetrahydropyrimidinones acting as HIV-1 protease inhibitors. A structural parameter, the first order valence molecular connectivity index ($^1\chi^v$), has been used to account for the variation in the activity. The protease inhibition activity as well as the antiviral potency of the compounds are found to be significantly correlated with $^1\chi^v$ of $P_2/P_{2'}$ substituents attached to the two nitrogens N1 and N3, suggesting that substituents containing less electronegative and more saturated atoms, meaning thereby the less polar or more hydrophobic substituents, will be more advantageous. Further, if P_2 and $P_{2'}$ are dissimilar, the former is found to be more effective than the latter. This difference is attributed to a conformational change in the enzyme that may be more favorable to P_2 binding than to $P_{2'}$ binding.

Introduction

The human immunodeficiency virus of type 1 (HIV-1), which is the causative agent of Acquired Immunodeficiency Syndrome (AIDS), encodes an aspartyl protease. This aspartyl protease is a homodimeric enzyme that cleaves the polyprotein products of the *gag* and *pol* viral genes, yielding structural proteins and enzymes that are essential to the life cycle of the virus. Inhibition of this enzyme leads to the production of non-infectious viral particles[1,2] and thus to the prevention of further propagation of the virus. Since abundant structural information is available on this enzyme, it has become an attractive target for computer-aided drug design strategies[3,4] and consequently a prime focus for the development of anti-HIV chemotherapy.

Certain series of compounds that were complementary to the C_2 symmetric HIV-1 protease were found to be potent inhibitors of this enzyme. Such compounds were, for example, seven-membered cyclic urea derivatives (**1**),[5–7] cyclic cyanoguanidines (**2**),[8] and tetrahydropyrimidinones (**3**).[9] These compounds create an effective hydrogen bond network between the aspartic residues and the flap region of the enzyme without the intervention of a water molecule commonly found in linear inhibitors. In order to get a deeper insight into the mechanism of interaction of such compounds with the receptor, quantitative structure–activity relationship (QSAR) studies have been made on some series of cyclic ureas and cyclic cyanoguanidines.[10–12] With the same objective, we want to report here a QSAR study on a few series of tetrahydropyrimidinones studied by De Lucca et al.[9] QSAR studies have greatly helped in discussing the mechanism of HIV-1 protease inhibition[12–15] and also of reverse transcriptase inhibition,[12,16–19] another strategy important in the development of anti-HIV chemotherapy, by different classes of inhibitors.

Materials and Methods

Two different series of tetrahydropyrimidinones as listed in Tables 1 and 2 are subjected to QSAR. These compounds were studied by De Lucca et al.[9] In the tables, K_i refers to the enzyme inhibition constant and IC_{90} is a measure of antiviral potency of the compound and refers to the molar concentration of the compound, required to reduce the concentration of HIV viral RNA by 90% from the level measured in an infected culture.

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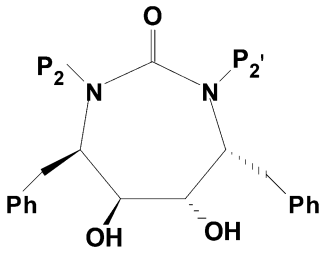

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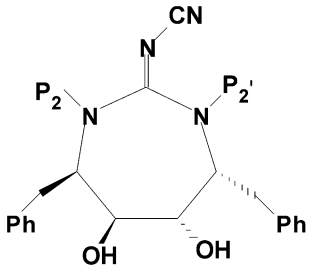

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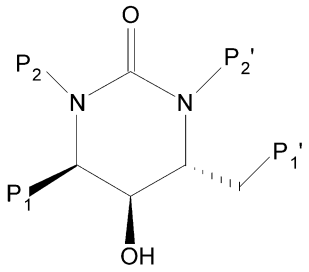

3 ($P_1/P_{1'}$=CH_2-Ph)

An attempt has been made to correlate these activity parameters with a structural parameter $^1\chi^v$, which is known as first order valence molecular connectivity index. This parameter signifies the degree of branching, connectivity of atoms, and the unsaturation in the molecule. It is defined as[20]

$$^1\chi^v = \Sigma\,(\delta_i^v\delta_j^v)^{-1/2} \quad (1)$$

where δ_i^v and δ_j^v are the vertex connectivity indices of atoms i and j, respectively, and the summation extends to all bonded pairs of atoms i and j. For second and third rows of atoms, a unified definition of δ^v, as expressed by eq (2), was given.[21]

$$\delta^v = \frac{(Z_i^v - h_i)}{(Z_i - Z_i^v - 1)} \quad (2)$$

In this equation, Z_i^v is the number of valence electrons of atom i, h_i is the number of hydrogen atoms attached to it, and Z_i is its atomic number. Using eqs (1) and (2), $^1\chi^v$ values were calculated only for the substituents.

Results and Discussion

For the 26 compounds of Table 1, the inhibition constant K_i was found to have a significant correlation, as shown by eq (3), with $^1\chi^v$ of $P_2/P_{2'}$ substituents and two indicator variables I_1 and I_2.

Table 1. A series of tetrahydropyrimidinones (**3**) with similar $P_2/P_{2'}$ substituents and their HIV-1 protease inhibition activity and antiviral potency along with structural parameters

					log(1/K_i)		log(1/IC_{90})	
Compd	$P_2/P_{2'}$	$^1\chi^v$	I_1	I_2	Obsd[9]	Calcd eq (4)	Obsd[9]	Calcd eq (5)
1	3-Cyanobenzyl	2.648	1	0	7.959	7.469	5.796	5.802
2	3-Cyanobenzyl	2.648	1	0	7.854	7.469	5.807	5.802
3	3-Cyano-4-fluorobenzyl	2.753	1	0	6.638	7.513	—	—
4	3-Acetyl benzyl	3.128	0	0	9.040	9.610	7.309	7.140
5	3-Hydroxymethylbenzyl	2.844	0	0	9.309	9.491	6.962	7.041
6	3-Carboxybenzyl	2.852	0	0	9.060	9.494	—	—
7	3-(Carboxamido)benzyl	2.917	0	0	10.045	9.521	7.445	7.067
8	3-(Carboxamido)benzyl[a]	2.917	0	0	9.508	9.521	7.445	7.067
9	3-(Carboxamido)benzyl[b]	2.917	0	0	9.823	9.521	7.045	7.067
10	3-(Carboxamido)-4-fluorobenzyl	3.023	0	0	8.853	9.566	6.309[d]	7.102
11	3-(Carboxamido oxime)benzyl	3.137	0	1	10.698	10.634	7.309	7.143
12	3-(Carboxamido oxime)benzyl[a]	3.137	0	1	10.698	10.634	7.309	7.143
13	3-(Carboxamido oxime)benzyl[b]	3.137	0	1	11.000	10.634	6.931	7.143
14	3-(Carboxamido oxime)-4-fluorobenzyl	3.326	0	1	10.221	10.714	7.292	7.209
15	3-Aminobenzyl	2.463	0	0	8.769	9.330	6.437	6.908
16	3-Amino-4-fluorobenzyl	2.569	0	0	9.602	9.375	7.443	6.945
17	4-Amino-3-fluorobenzyl	2.569	0	0	8.096[c]	9.375	6.268	6.945
18	3-(*N*-Methyl-amino)benzyl	2.924	0	0	8.309[c]	9.524	6.484	7.069
19	3-(Pyrazol-3yl)benzyl	3.782	0	0	10.000	9.886	7.657	7.368
20	Indazol-5-yl-methyl	3.112	0	0	10.698[c]	9.603	8.221[d]	7.133
21	Indazol-6-yl-methyl	3.112	0	0	10.221	9.604	7.292	7.134
22	(3-Methylindazol-5-yl)-methyl	3.577	0	0	10.000	9.799	7.744	7.296
23	3-Aminoindazol-5-yl-methyl	3.366	0	0	10.522[e]	9.711	6.416[d,e]	7.221
24	3-Aminobenzisoxazol-5-yl-methyl	3.240	0	0	9.387	9.657	6.879	7.179
25	3-(5-Methyl-2-pyridilcarboxamido)-benzyl	5.301	0	0	10.096	10.525	7.585	7.897
26	3-(*N*-2-Thiazolylcarboxamido)-benzyl	4.396	0	0	10.522	10.144	7.508	7.582

[a]The $P_1/P_{1'}$ phenyl groups contain a 4-fluoro substituent.
[b]The $P_1/P_{1'}$ phenyl groups contain a 3,4-difluoro substituent.
[c]Not used in the derivation of eq (4).
[d]Not used in the derivation of eq (5).
[e]Not used in the derivation of eq (9).

$$\log(1/K_i) = 0.548(\pm0.456)^1\chi^v - 1.798(\pm0.854)I_1 + 1.097(\pm0.725)I_2 + 7.811(\pm1.497)$$
$$n = 26,\ \ r = 0.833,\ \ s = 0.64,\ \ F_{3,22} = 16.60(4.82) \quad (3)$$

The variable I_1 stands, with a value of 1, for a $P_2/P_{2'}$ substituent that contains a CN group at the phenyl ring. Similarly, the variable I_2 stands, with a value of 1, for a $P_2/P_{2'}$ substituent that contains a C(NH_2)=N–OH group at the phenyl ring. In eq (3), n is the number of data points, r is the correlation coefficient, s is the standard deviation, F is the F-ratio between the variances of calculated and observed activities, and the figures within the parentheses with ±sign are the 95% confidence intervals. The F-value given in parenthesis is of 99% level. Eq (3) suggests that the connectivity of $P_2/P_{2'}$ substituent has to play a positive role in the inhibition of the protease. The increase in connectivity value will lead to an increase in the inhibition potency of the compound. If we look at eq (1), we find that the connectivity will increase if δ^v decreases. Eq (2) suggests that δ^v will decrease if Z_i^v decreases and/or h_i increases, meaning thereby that less electronegative and more saturated atoms may have smaller δ^v values. A group or molecule, thus, containing less electronegative and more saturated atoms would be beneficial to the activity, as it will have higher $^1\chi^v$ value. However, a highly negative coefficient of variable I_1 indicates that a CN-containing $P_2/P_{2'}$ substituent would produce an adverse effect. This can be attributed to some steric effects that might be produced by CN.

However, a highly positive coefficient of I_2 suggests that a substituent having C(NH_2)=N–OH group would be highly conducive to the activity. This group may be assumed to form two strong hydrogen bonds, through its both NH_2 and OH moieties, with the receptor and thus highly strengthen the drug-receptor binding. This ability of hydrogen bond formation of this group might dominate its steric effects, if any.

Compounds 17, 18, and 20 had exhibited highly aberrant behavior in eq (3). Therefore, when these three compounds were excluded, a much better correlation was obtained [eq (4)]. With exclusion of certain outliers (10, 20, and 23), a satisfactory correlation was found to exist between the antiviral activity (IC_{90}) and the $^1\chi^v$ and I_1 [eq (5)]. The variable I_2 was not found to be significant in this case.

$$\log(1/K_i) = 0.421(\pm0.378)^1\chi^v - 1.939(\pm0.700)I_1 + 1.020(\pm0.590)I_2 + 8.293(\pm1.266)$$
$$n = 23,\ \ r = 0.895,\ \ s = 0.50,\ \ F_{3,19} = 25.37(5.01) \quad (4)$$

$$\log(1/IC_{90}) = 0.348(\pm0.258)^1\chi^v - 1.171(\pm0.566)I_1 + 6.050(\pm0.849)$$
$$n = 21,\ \ r = 0.817,\ \ s = 0.35,\ \ F_{2,18} = 18.02(6.01) \quad (5)$$

The variable I_2 did not surface significant for binding constant, too, for the compounds of Table 2. In these compounds P_2 and $P_{2'}$ substituents were not identical, hence $^1\chi^v$ values were calculated for both P_2 and $P_{2'}$ separately, and both the biological parameters K_i and IC_{90} were found to be significantly correlated with $^1\chi^v$ and I_1 alone as

$$\log(1/K_i) = 0.862(\pm0.235)^1\chi^v(P_2) + 0.438(\pm0.153)^1\chi^v(P_{2'}) - 1.398(\pm0.600)I_1 + 5.840(\pm0.76)$$
$$n = 25,\ \ r = 0.906,\ \ s = 0.57,\ \ F_{3,21} = 32.22(4.87) \quad (6)$$

$$\log(1/IC_{90}) = 0.771(\pm0.609)^1\chi^v(P_2) + 0.534(\pm0.150)^1\chi^v(P_{2'}) - 0.932(\pm0.855)I_1 + 3.452(\pm2.038)$$
$$n = 15,\ \ r = 0.925,\ \ s = 0.37,\ \ F_{3,11} = 21.69(6.22) \quad (7)$$

Eqs (6) and (7) represent quite parallel correlations, which suggest that there can be a good parallelism between K_i and IC_{90} data, and, of course, the regression analysis was found to reveal quite significant correlation between the two [eq (8)] and not only in this case but also for the series of Table 1 [eq (9)].

$$\log(1/IC_{90}) = 1.102(\pm0.358)\log(1/K_i) + 1.890(\pm3.405)$$
$$n = 15,\ \ r = 0.874,\ \ s = 0.43,\ \ F_{1,13} = 42.14(9.07) \quad (8)$$

$$\log(1/IC_{90}) = 0.539(\pm0.175)\log(1/K_i) + 1.890(\pm1.688)$$
$$n = 23,\ \ r = 0.813,\ \ s = 0.37,\ \ F_{1,21} = 41.00(8.02) \quad (9)$$

However, it should be noted that the coefficient of $\log(1/K_i)$ is much larger in eq (8) than in eq (9). It leads to suggest that the translation of the enzyme inhibition activity to antiviral potency is more sensitive for the compounds of Table 2, where P_2 and $P_{2'}$ are dissimilar, than for the compounds of Table 1, where P_2 and $P_{2'}$ are similar.

For IC_{90} of Table 2, a much improved correlation was obtained when compound 18, showing slightly aberrant behavior, was excluded [eq (10)].

$$\log(1/IC_{90}) = 1.199(\pm0.482)^1\chi^v(P_2) + 0.596(\pm0.108)^1\chi^v(P_{2'}) - 0.942(\pm0.578)I_1 + 2.088(\pm1.592)$$
$$n = 14,\ \ r = 0.970,\ \ s = 0.25,\ \ F_{3,10} = 53.40(6.55) \quad (10)$$

It is to be noticed that in both eqs (6) and (7) the coefficient of $^1\chi^v$ (P_2) is larger than that of $^1\chi^v$ ($P_{2'}$), meaning thereby that P_2 substituent has better effect than $P_{2'}$. This difference is more prominent in eq (10). The reason

Table 2. A series of tetrahydropyrimidinones (**3**) with dissimilar $P_2/P_{2'}$ substituents and their structural parameters

Compd	P_2	$P_{2'}$	$^1\chi^v$ (P_2)	$^1\chi^v$ ($P_{2'}$)	I_1
1	H	H	0.000	0.000	0
2	Benzyl	H	2.580	0.000	0
3	3-Cyanobenzyl	H	2.964	0.000	1
4	3-Cyano-4-fluorobenzyl	H	3.070	0.000	1
5	3-Hydroxybenzyl	H	2.714	0.000	0
6	3-Aminobenzyl	H	2.779	0.000	0
7	3-(Carboxamido)benzyl	H	3.233	0.000	0
8	3-(Carboxamido)-4-fluorobenzyl	H	3.339	0.000	0
9	3-(Carboxamido oxime) benzyl	H	3.453	0.000	0
10	3-Aminoindazol-5-yl-methyl	H	3.682	0.000	0
11	Indazol-5-yl-methyl	H	3.428	0.000	0
12	H	Indazol-5-yl-methyl	0.000	3.428	0
13	H	3-Aminobenzyl	0.000	2.779	0
14	Benzyl	3-Cyano-4-fluorobenzyl	2.580	3.070	1
15	3-Cyano-4-fluorobenzyl	Benzyl	3.070	2.580	1
16	3-(Carboxamido oxime)benzyl	Cyclopropylmethyl	3.453	2.041	0
17	Benzyl	3-Aminoindazol-5-yl-methyl	2.580	3.682	0
18	3-Aminoindazol-5-yl-methyl	Benzyl	3.682	2.580	0
19	Indazol-5-yl-methyl	3-Aminobenzyl	3.428	2.779	0
20	3-Aminobenzyl	Indazol-5-yl-methyl	2.779	3.428	0
21	3-Aminobenzyl	3-Methylindazol-5-yl-methyl	2.779	3.894	0
22	3-Aminobenzyl	3-Cyanobenzyl	2.779	2.965	1
23	3-Aminobenzyl	3-Aminoindazol-5-yl-methyl	2.779	3.682	0
24	3-Aminobenzyl	3-(Carboxamido)benzyl	2.779	3.233	0
25	3-Aminobenzyl	3-(Carboxamido oxime)benzyl	2.779	3.453	0

for this difference can be due to a better involvement in binding of P_2 than of $P_{2'}$ with the receptor. Such a speculation was made in the case of cyanoguanidines (**2**) also,[8,11] where however both P_2 and $P_{2'}$ were identical. Now it can be assumed that compounds like cyanoguanidines (**2**) or tetrahydropyrimidinones (**3**) might bring a conformational change in the enzyme such that only one of the P_2 and $P_{2'}$ substituents may have a better opportunity to bind with the active sites of the enzyme.

As resistant variants may emerge more quickly against symmetric inhibitors[22] and as the translation of the enzyme inhibition activity to antiviral potency is found to be less sensitive for symmetric molecules, as in the present case, the asymmetric inhibitors may be preferred.

As already discussed, less electronegative and more saturated atoms in a group or molecule may lead to higher $^1\chi^v$ value. Such atoms may have small electronegativity difference and thus may be less polarizable. Groups or molecules containing such atoms may be, therefore, less polar and consequently more hydrophobic in nature. It has not been surprising, therefore, that excellent correlations have been found between the connectivity indices and the hydrophobic properties of varying groups of compounds.[20] Therefore, one can assume that in the present case the P_2 and $P_{2'}$ substituents might have hydrophobic interactions with the receptor sites. In the case of cyclic ureas (**1**) and cyclic cyanoguanidines (**2**), the antiviral activities were shown to be correlated with only hydrophobic property of P_2 and $P_{2'}$ substituents. However, it is difficult to evaluate theoretically the exact value of the hydrophobic parameter (log P) of a group or molecule and the experimental value of log P (P: octanol–water partition coefficient) of a desired group or molecule is not always easily accessible. Hence, the use of $^1\chi^v$ can be preferred.

Table 3. HIV-1 protease inhibition activity and antiviral potency data of compounds of Table 2

	$\log(1/K_i)$		$\log(1/IC_{90})$		
Compd	Obsd[9]	Calcd eq (6)	Obsd[9]	Calcd eq (7)	Calcd eq (10)
1	6.013	8.064	—	—	—
2	7.180	5.840	—	—	—
3	7.823	6.998	—	—	—
4	6.958	7.089	—	—	—
5	8.585	8.180	5.318	5.545	5.343
6	8.207	8.236	5.363	5.595	5.421
7	8.251	8.627	—	—	—
8	7.853	8.719	—	—	—
9	9.619	8.817	6.431	6.115	6.229
10	9.420	9.014	6.260	6.292	6.504
11	8.920	8.795	6.229	6.096	6.199
12	7.356	7.342	—	—	—
13	6.804	7.058	—	—	—
14	7.481	8.011	—	—	—
15	7.397	8.219	—	—	—
16	9.318	9.711	7.443	7.205	7.446
17	9.187	9.677	7.148	7.408	7.378
18	9.552	10.144	6.899[a]	7.669	—
19	10.096	10.013	7.886	7.580	7.857
20	10.000	9.737	7.795	7.426	7.465
21	9.886	9.942	7.494	7.675	7.743
22	8.795	8.137	6.247	6.247	6.247
23	10.000	9.849	7.275	7.561	7.617
24	10.221	9.652	7.619	7.322	7.349
25	10.698	9.748	7.769	7.439	7.480

[a]Not used in the derivation of eq (10).

However, since $^1\chi^v$ is also a measure of the size of the molecule,[20] a correlation with $^1\chi^v$ can also describe the van der Waals interaction. Whatsoever, in the present case, the hydrophobic interaction is more likely than van der Waals interaction since in cyclic ureas and cyclic cyanoguanidines, which are similar to tetrahydropyrimidinones, the involvement of hydrophobic interaction was exhibited.[10,11]

Now, as a conclusion it can be said that P_2 and $P_{2'}$ substituents in tetrahydropyrimidinones may have the hydrophobic interactions with the receptor, with the former having a dominant effect. A hydrogen bond forming group, like OH or NH_2, on these substituents may have an added effect through the formation of hydrogen bonds with the receptor. Hydrogen bondings, in fact, play very dominant role in HIV-1 protease inhibition. In tetrahydropyrimidinones, the carbonyl oxygen of position 2 and the hydroxyl group of position 5 may constitute the constant sites for hydrogen bondings.

Like P_2 and $P_{2'}$ substituents, P_1 and $P_{1'}$ substituents may also have hydrophobic interactions with the receptor.

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