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QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIP STUDIES ON CYCLIC UREA-BASED HIV PROTEASE INHIBITORS

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A quantitative structure–activity relationship (QSAR) study is described on some cyclic ureas that inhibit the enzyme HIV-1 protease (HIV-1-PR) and exhibit antiviral potency. Both the enzyme inhibition activity and the antiviral potency were found to be primarily governed by the hydrophobic property of the substituents at the nitrogens (N2/N2′) of the urea. Adjacent to the nitrogens, the C1/C1′-substituents are, however, found to affect the activity (inhibition) by their molecular size. The essential binding of the ureas with the receptor is, however, through multiple hydrogen bonding, where the substituents, too, can participate in such binding if they are capable of doing so. A schematic diagram of the overall interaction of the inhibitors with the receptor is presented.

Keywords: Quantitative structure–activity relationship; HIV-1 protease inhibitors; Cyclic urea derivatives; QSAR

INTRODUCTION

The human immunodeficiency virus (HIV) is a pathogenic retrovirus and causative agent of Acquired Immunodeficiency Syndrome (AIDS) and its related disorders. Therefore, it has become a pressing goal of contemporary medicinal chemists to find potent and effective drugs against HIV, particularly HIV-1, the most common form of the virus. Though the development of anti-HIV drugs faces problems since the retrovirus gets permanently integrated in the cellular chromosomes in the form of proviral DNA, a variety of molecular targets are available for chemotherapeutic intervention in the

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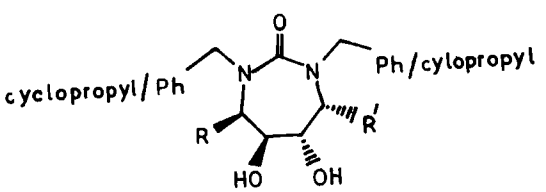
unique replication cycle of HIV-1. An attractive target is the HIV-encoded protease (HIV-1-PR), which has been shown to be essential for viral maturation and infectivity. The inhibition of HIV-1-PR in vitro results in the production of progeny virions, which are immature and noninfectious.[1,2] Since much 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.[5] However, the developments of anti-HIV chemotherapy based on HIV-PR inhibition will always be an ongoing need, because the virus has the ability to rapidly generate resistant mutants.[6,7] Therefore, some authors have recently paid attention to cyclic urea-based HIV-1-PR inhibitors,[8–10] which create an efficient hydrogen bond network between the asparate residues and the flap region of the enzyme without the intervention of a water molecule commonly found in linear inhibitors.[3] To aid in the design, in this class, of inhibitors with superior pharmacokinetic and efficacy profiles, we have made a quantitative structure–activity relationship (QSAR) study on some series of cyclic urea derivatives.

MATERIALS AND METHOD

The two large series of cyclic urea derivatives (**1**, **2**) studied for their HIV-1-PR inhibition activity and antiviral potency by Nugiel *et al.*[9] and by Lam *et al.*[10] were compiled and listed in Tables I and II. The enzyme inhibition activity was reported in terms of K_i, the inhibition constant, and the antiviral



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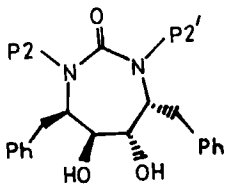

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potency in terms of IC_{90}, the molar concentration of the compound required to reduce the concentration of HIV viral RNA by 90% from the level measured in an infected culture. A Hansch analysis was performed on these activities of the compounds to find out the correlation between them and the physicochemical properties of the substituents. We have recently reported[11–14] excellent correlations between the physicochemical properties

and the reverse transcriptase inhibition activity for different series of compounds. The enzyme reverse transcriptase (RT) forms another molecular target in the life cycle of HIV-1 for the development of chemotherapy of HIV infection. A combination of HIV-PR and RT inhibitors may have much improved effects in AIDS therapy. Under clinical settings, three HIV-PR inhibitors, recently approved by the FDA for AIDS treatment in combination with RT inhibitors, have been shown to reduce the viral load and increase the number of $CD4^+$ lymphocytes in HIV-infected patients.[15]

RESULTS AND DISCUSSION

Let us first consider the series of compounds belonging to **1** (Table I). In this series, for the first 26 compounds, the N2/N2′-substituent (P2/P2′) is the benzyl group and, for the remaining compounds (27–38), it is a cyclopropylmethyl group. Thus, the series can be divided into two groups: Group A, containing compounds 1–26, and Group B, containing compounds 27–38. When a regression analysis was performed initially for Group A, a significant correlation was obtained (Eq. (1)) between the enzyme inhibition activity and the van dar Waals volume of the R/R′-substituent and two indicator parameters I_a and I_o.

$$\log(1/K_i) = 5.741(\pm 3.221)V_w - 2.592(\pm 1.414)V_w^2 + 1.542(\pm 0.708)I_a - 1.010(\pm 0.774)I_o + 3.646,$$
$$n = 24, \quad r = 0.89, \quad s = 0.48, \quad F_{4,19} = 18.58\ (4.50). \tag{1}$$

The indicator parameter I_a has been used, with a value of unity, for a substituent containing aromatic moiety, and I_o has been used, with a value of unity, for an ortho-substituent in the latter. In the equation, n is the number of data points, r is the correlation coefficient, s is the standard deviation, F is F-ratio between the variances of calculated and observed activities, and data within the parentheses preceding the variables are 95% confidence intervals. The value of F given in the parenthesis is of 99% level. All these parameters show that the correlation is statistically quite significant, suggesting that the molecular size of the R/R′-substituent would be an important factor in the protease inhibition and that an aromatic substituent will have an added advantage but an ortho-substituent in it will have a detrimental effect.

TABLE I Cyclic urea derivatives (**1**), their HIV-1 protease inhibition activity and antiviral potency studied, by Nugiel *et al.*[9] and their physicochemical parameters

S.No.	*R/R'*	V_w^a	I_a	I_o	log(1/K_i)		log(1/IC_{90})
					Obsd.[b]	*Calcd. Eq.* (2)	*Obsd.*
N2,N2'-dibenzyl derivatives							
1	benzyl	0.94	1	0	8.41	8.34	6.10
2	methyl	0.25	0	0	5.30	5.03	—
3	4-isopropylbenzyl	1.40	1	0	8.96	8.19	—
4	4-(methylthio)benzyl	1.28	1	0	8.47	8.33	5.89
5	isobutyl	0.71	0	0	5.77	6.41	—
6	2-(methylthio)ethyl	0.73	0	0	5.96	6.45	—
7[c]	3-indolylmethyl	1.12	1	0	6.24	8.37	—
8	cyclohexylmethyl	1.07	0	0	7.55	6.78	—
9[c]	phenethyl	1.08	1	0	6.50	8.37	—
10	2-napthylmethyl	1.36	1	0	8.01	8.25	5.48
11	3-furanylmethyl	0.76	1	0	8.08	8.12	5.11
12	3-(methylthio)benzyl	1.28	1	0	8.00	8.33	5.38
13	4-(methylthiosulfonyl)benzyl	1.40	1	0	8.60	8.20	6.33
14	2-methoxybenzyl	1.17	1	1	7.22	7.29	5.06
15	2-hydroxybenzyl	1.01	1	1	7.46	7.28	5.19
16	3-methoxybenzyl	1.17	1	0	8.33	8.39	6.46
17	4-methoxybenzyl	1.17	1	0	8.07	8.39	6.22
18	4-hydroxybenzyl	1.01	1	0	8.96	8.38	6.73
19	3-aminobenzyl	1.04	1	0	8.55	8.39	5.89
20	3-(dimethylamino)benzyl	1.36	1	0	8.37	8.24	5.92
21	4-aminobenzyl	1.04	1	0	8.07	8.39	5.85
22	4-aminobenzyl.2HCl	1.04	1	0	8.15	8.39	5.89
23	4-(dimethylamino)benzyl	1.36	1	0	7.34	8.24	5.57
24	4-pyridylmethyl	0.90	1	0	7.65	8.30	5.24
25	3-(2,5-dimethylpyrolyl)benzyl	1.80	1	0	6.80	7.26	—
26	3,4-(methylenedioxy)benzyl	1.15	1	0	8.89	8.40	6.30
N2,N2'-bis(cyclopropylmethyl) derivatives							
27	benzyl	0.94	1	0	8.72	8.34	5.74
28	isobutyl	0.71	0	0	7.07	6.41	—
29	isopropyl	0.55	0	0	6.60	6.06	—
30	2-(methylthio)ethyl	0.73	0	0	5.60	6.45	—
31	4-fluorobenzyl	0.99	1	0	8.24	8.37	5.50
32	2-methoxybenzyl	1.17	1	1	7.19	7.29	—
33	3-methoxybenzyl	1.17	1	0	9.06	8.39	6.19
34	3-hydroxybenzyl	1.01	1	0	7.89	8.38	5.59
35	4-methoxybenzyl	1.17	1	0	8.54	8.39	6.50
36	2-napthylmethyl	1.36	1	0	8.37	8.25	5.47
37	3,5-dimethoxybenzyl	1.41	1	0	8.57	8.18	6.42
38	2-thienylmethyl	0.87	1	0	8.04	8.27	5.11

[a] Calculated as suggested by Moriguchi, I. *et al.* (1976) *Chem. Pharm. Bull. (Tokyo)*, **24**, 1799–1806. [b] From Ref. 9. [c] Not included in the derivation of Eq. (1).

In the derivation of Eq. (1), however, compounds 7 and 9 were not included, as they exhibited an aberrant behaviour. The activity values of these compounds as predicted by Eq. (1) were much higher than their corresponding observed values (8.37 vs 6.24 and 8.37 vs 6.50). The reason for the

low observed activities of these two compounds may be due to some steric effects produced by the substituents or the misorientation of the substituents towards the active site of the receptor.

Equation 1 beautifully absorbs all the 12 compounds of Group B, maintaining essentially all its statistical and analytical characteristics (Eq. (2)).

$$\log(1/K_i) = 5.567(\pm 2.984)V_w - 2.491(\pm 1.308)V_w^2 + 1.527(\pm 0.606)I_a - 1.101(\pm 0.602)I_o + 3.767,$$
$$n = 36, \quad r = 0.89, \quad s = 0.48, \quad F_{4,31} = 28.79\ (4.00). \tag{2}$$

$$\log(1/K_i) = 5.465(\pm 3.024)V_w - 2.431(\pm 1.331)V_w^2 + 1.538(\pm 0.612)I_a - 1.100(\pm 0.608)I_o - 0.127(\pm 0.357)D + 3.878,$$
$$n = 36, \quad r = 0.89, \quad s = 0.48, \quad F_{5,30} = 22.79\ (3.70). \tag{3}$$

Equation (3) was derived to see the effect of an alteration in the N2/N2′-substituent, using a dummy variable D with a value of 1 for Group A, where this substituent is a benzyl group, and with a value of zero for Group B, where this substituent is a cyclopropylmethyl group. As is obvious from this equation, the D parameter was totally insignificant, suggesting that a variation in this substituent was of no consequence.

We were, however, unable to correlate so significantly the antiviral activity (IC_{90}) of these compounds with any physicochemical parameters. However, for the series of compounds belonging to **2** (Table II), where the variation is in the N2/N2′-substituent, the IC_{90} data were found to be significantly correlated with the hydrophobic property of the substituents and some indicator variables (Eq. (4)). The indicator variable $I_H = 1$ is meant for the

$$\log(1/IC_{90}) = 2.531(\pm 0.899)\pi - 0.534(\pm 0.212)\pi^2 + 2.010(\pm 0.422)I_H - 0.749(\pm 0.493)I_o + 2.774,$$
$$n = 40, \quad r = 0.90, \quad s = 0.40, \quad F_{4,35} = 35.66\ (3.91). \tag{4}$$

last 5 compounds (50–54), which differ from the others in that they have an OH or NH_2 group in their N2/N2′-substituent. The variable $I_o = 1$ is meant for a benzyl substituent bearing a group at the ortho-position.

In the derivation of Eq. (4), compound 3 was, however, found to be a misfit. The exclusion of this compound led relatively to a much better

TABLE II Cyclic urea derivatives (**2**), their HIV-1 protease inhibition activity and antiviral potency studied by Lam *et al.*[10] and their physicochemical parameters

S.No.	*P2/P2′*	π[a]	I_H	I_o	I_e	log(1/K_i)			log(1/IC_{90})	
						Obsd.[b]	*Calcd. Eq.* (6)	*Calcd. Eq.* (7)	*Obsd.*[b]	*Calcd. Eq.* (5)
1[c]	methyl	0.65	0	0	0	5.24	6.63	—	—	—
2	n-ethyl	1.18	0	0	0	7.00	7.61	7.81	—	—
3[d]	n-propyl	1.71	0	0	0	8.10	8.24	8.34	4.27	—
4	n-butyl	2.24	0	0	0	8.85	8.53	8.53	6.17	5.85
5	n-pentyl	2.77	0	0	0	8.80	8.48	8.38	5.82	5.73
6	n-hexyl	3.30	0	0	0	8.34	8.08	7.89	—	—
7	n-heptyl	3.83	0	0	0	6.59	7.34	7.06	—	—
8	$CH_2CH_2OCH_3$	0.88	0	0	1	6.10	5.82	5.67	—	—
9	$CH_2CH_2OCH_2CH_3$	1.41	0	0	1	5.96	6.65	6.40	—	—
10	$CH_2CH_2OCH_2CH_2OCH_3$	0.95	0	0	1	5.11	5.94	5.78	—	—
11[c]	i-butyl	2.11	0	0	0	7.31	8.49	—	—	—
12	i-pentyl	2.64	0	0	0	7.92	8.52	8.46	5.50	5.79
13	i-hexyl	3.17	0	0	0	8.16	8.21	8.04	5.09	5.42
14	i-heptyl	3.70	0	0	0	7.52	7.55	7.30	—	—
15	i-octyl	4.23	0	0	0	6.96	6.55	6.22	—	—
16	neohexyl	3.04	0	0	0	7.44	8.32	8.17	—	—
17	allyl	1.23	0	0	0	8.28	7.68	7.86	5.33	5.16
18	2-methylpropen-3-yl	1.63	0	0	0	8.14	8.16	8.27	5.12	5.58
19	isoprenyl	2.54	0	0	0	8.75	8.54	8.48	6.06	5.82
20	$CH_2CH_2OCH{=}CH_2$	1.40	0	0	1	7.22	6.64	6.39	—	—
21	3-propynyl	0.75	0	0	0	7.66	6.85	7.13	4.38	4.42
22	cyclopropylmethyl	1.63	0	0	0	8.68	8.16	8.27	5.75	5.58
23	cyclobutylmethyl	2.18	0	0	0	8.89	8.52	8.52	6.00	5.85
24	cyclopentylmethyl	3.02	0	0	0	8.38	8.33	8.19	5.77	5.56
25	cyclohexylmethyl	3.31	0	0	0	7.43	8.07	7.88	—	—
26	N-morpholino-2-ethyl	0.87	0	0	1	5.40	5.80	5.65	—	—
27	benzyl	2.27	0	0	0	8.52	8.54	8.53	6.08	5.86
28	2-picolyl	0.78	0	0	0	6.84	6.90	7.17	4.31	4.47
29[c]	3-picolyl	0.78	0	0	0	8.01	6.90	—	5.06	4.47
30	4-picolyl	0.78	0	0	0	7.05	6.90	7.17	4.01	4.47
31	α-napthylmethyl	3.45	0	0	0	7.07	7.90	7.69	4.80	5.08
32[c]	β-napthylmethyl	3.45	0	0	0	9.51	7.90	—	5.41	5.08
33	*o*-flurobenzyl	2.42	0	1	0	7.47	7.11	7.26	5.26	5.04
34	*m*-fluorobenzyl	2.42	0	0	0	8.52	8.55	8.51	6.15	5.85
35	*p*-fluorobenzyl	2.42	0	0	0	8.85	8.55	8.51	6.22	5.85
36	*o*-chlorobenzyl	2.99	0	1	0	6.62	6.91	6.97	4.95	4.77
37	*m*-chlorobenzyl	2.99	0	0	0	9.05	8.35	8.22	5.89	5.58
38	*p*-chlorobenzyl	2.99	0	0	0	8.28	8.35	8.22	5.35	5.58
39	*m*-bromobenzyl	3.14	0	0	0	8.85	8.23	8.07	5.92	5.45
40	*p*-bromobenzyl	3.14	0	0	0	7.57	8.23	8.07	5.09	5 45
41	*m*-methylbenzyl	2.80	0	0	0	8.16	8.46	8.36	5.62	5.71
42	*p*-methylbenzyl	2.80	0	0	0	8.25	8.46	8.36	5.37	5.71
43	*m*-(trifluoromethyl)benzyl	3.16	0	0	0	7.66	8.22	8.05	5.11	5.51
44	*p*-(trifluoromethyl)benzyl	3.16	0	0	0	7.29	8.22	8.05	5.14	5.51
45	*o*-methoxybenzyl	2.19	0	1	1	5.73	5.80	5.59	4.64	5.04
46[c]	*m*-methoxybenzyl	2.19	0	0	1	8.80	7.24	—	5.89	5.85
47	*p*-methoxybenzyl	2.19	0	0	1	6.81	7.24	6.84	5.12	5.85
48	*m*-nitrobenzyl	2.02	0	0	0	8.55	8.45	8.49	6.01	5.81
49[c]	*m*-iodobenzyl	3.40	0	0	0	9.38	7.96	—	5.52	5.15

TABLE II (*Continued*)

S.No.	*P2/P2'*	π[a]	I_H	I_o	I_e	log(1/K_i)			log(1/IC_{90})	
						Obsd.[b]	*Calcd. Eq.* (6)	*Calcd. Eq.* (7)	*Obsd.*[b]	*Calcd. Eq.* (5)
50	*p*-(hydroxymethyl)benzyl	1.24	1	0	0	9.47	9.62	9.64	7.22	7.25
51	*m*-(hydroxymethyl)benzyl	1.24	1	0	0	9.85	9.62	9.64	7.42	7.25
52	*p*-hydroxybenzyl	1.61	1	0	0	9.92	10.08	10.02	7.50	7.48
53	*m*-hydroxybenzyl	1.61	1	0	0	9.92	10.08	10.02	7.27	7.48
54	*m*-(aminobenzyl).2CH_3SO_2H	1.05	1	0	0	9.55	9.33	9.38	6.89	6.83

[a] Calculated according to Hansch, C. and Leo, A.J. (1979) *Substituent Constants for Correlation Analysis in Chemistry and Biology*, John-Wiley, New York. [b] From Ref. 10. [c] Not used in the derivation of Eq. (7). [d] Not used in the derivation of Eq. (5).

correlation (Eq. (5)).

$$\log(1/IC_{90}) = 2.732(\pm 0.759)\pi - 0.592(\pm 0.180)\pi^2 + 1.914(\pm 0.357)I_H - 0.810(\pm 0.414)I_o + 2.705,$$
$$n = 39, \quad r = 0.93, \quad s = 0.33, \quad F_{4,34} = 50.80\ (3.93). \qquad (5)$$

So far as the enzyme inhibition activity was concerned, the most relevant equation obtained for that was:

$$\log(1/K_i) = 2.966(\pm 1.002)\pi - 0.612(\pm 0.224)\pi^2 + 1.929(\pm 0.690)I_H - 1.440(\pm 0.832)I_o - 1.279(\pm 0.572)I_e + 4.963,$$
$$n = 54, \quad r = 0.85, \quad s = 0.67, \quad F_{5,48} = 23.92\ (3.42). \qquad (6)$$

In this equation, I_e is an additional parameter, which has been used for ethereal substituents including those having a methoxy group. The negative coefficient of this parameter suggests that such substituents are not conductive to good activity.

Although Eq. (6) predicts for certain compounds very high or very low activity as compared correspondingly to their observed activity, giving a difference of 1 log unit (see Table II, high activity for compounds 1 and 11 and low activity for compounds 29, 32, 46 and 49), it expresses statistically a quite significant correlation, accounting overall for 72% of the variance in the activity ($r^2 = 0.72$). If these six compounds, which are misfit in the correlation are excluded, a highly improved correlation as expressed by Eq. (7) is obtained.

$$\log(1/K_i) = 2.751(\pm 0.771)\pi - 0.606(\pm 0.166)\pi^2 + 1.766(\pm 0.486)I_H - 1.251(\pm 0.603)I_o - 1.680(\pm 0.436)I_e + 5.400,$$
$$n = 48, \quad r = 0.93, \quad s = 0.46, \quad F_{5,42} = 51.78\ (3.49). \qquad (7)$$

Thus Eqs. (4)–(7) suggest that both the antiviral and the enzyme inhibition activities of the compounds are governed by the hydrophobic property of the N2/N2′-substituent with an almost equal optimum value of π, 2.31 for the former (Eq. (5)) and 2.27 for the latter (Eq. (7)), and that in both the cases, an OH- or NH_2-containing substituent would be of more advantage. This leads us to assume that N2/N2′-substituents may have predominantly a hydrophobic interaction with the receptor and that the presence of an OH or NH_2 group in them may be involved in effective hydrogen bonding with the receptor.

In both the cases, it is however also indicated that an ortho-substituted benzyl group will produce an adverse effect. This adverse effect can be attributed to some steric role of the ortho substituent. In the case of the enzyme inhibition, an ethereal substituent is also found to produce a negative effect, which can be attributed to the repulsive effects of lone pairs of electrons at the oxygen.

The similarity of the effects in this series on the antiviral and enzyme inhibition activities is due to the fact that both the activities are mutually well correlated ($n = 40$, $r = 0.82$).

The main interaction of cyclic urea inhibitors with HIV-PR, however, involves multiple hydrogen bonds. The high resolution structural studies on the complexes of HIV-1-PR with peptidomimetic inhibitors have revealed the presence of a structural water molecule which is hydrogen bonded to both

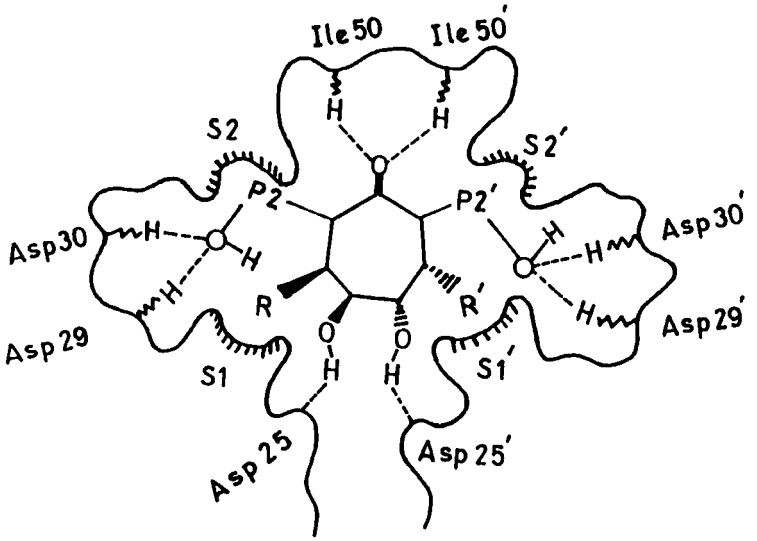

FIGURE 1 Schematic representation of the interaction of cyclic ureas with HIV-1 proteases.

the mobile flaps of the enzyme and the two carbonyls flanking the transition-state mimic of the inhibitors.[10] Cyclic ureas incorporate this structural water and preorganize the side chain residues into optimum binding conformations. They undergo reasonably symmetrical binding with the enzyme. The urea oxygen accepts two hydrogen bonds from the backbone of NH of Ile50/50′ and the diols form multiple hydrogen bonds with catalytic Asp25/25′. The OH or NH_2 present in the N2/N2′-substituent is supposed to be involved in hydrogen bonding with the backbone NH of Asp29/29′ and Asp30/30′. A schematic representation of the bindings is given in Figure 1, where the N2/N2′-substituents project symmetrically into S2/S2′ pockets of the enzyme for hydrophobic interaction, and the R/R′-substituents into the S1/S1′ pockets, most likely for dispersion interaction.

Acknowledgements

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