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# Quantitative Structure–Activity Relationship Studies on Cyclic Cyanoguanidines Acting as HIV-1 Protease Inhibitors

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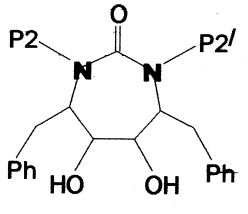
**Abstract**—A quantitative structure–activity relationship study has been performed on some cyclic cyanoguanidines that inhibit the enzyme HIV-1 protease (HIV-1-PR) and exhibit antiviral potency, and the results have been compared with those of cyclic urea derivatives. Both the enzyme inhibition activity and antiviral potency in cyclic cyanoguanidines as well as in cyclic urea derivatives are found to be primarily governed by hydrophobic property of substituents attached to nitrogen (P2/P2′) and further enhanced by OH or $NH_2$ group, if any, present in the substituents. However, aromatic substituents are found to be unfavourable to both the activities of cyclic cyanoguanidines but not to any activity of cyclic urea derivatives. Cyclic urea derivatives are indicated to be more potent than cyclic cyanoguanidines. A model for the interaction of cyclic cyanoguanidines with the receptor is proposed. 

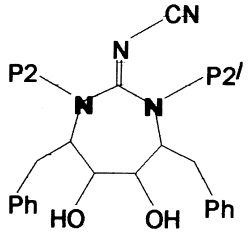
## Introduction

Acquired immunodeficiency syndrome (AIDS) is a life threatening and degenerative disease of the immune system caused by a retrovirus known as human immunodeficiency virus of type 1 (HIV-1). The aspartyl protease (PR) of HIV-1 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 protease leads to the production of non-infectious viral particles[1,2] and thus the prevention of further propagation of the virus. Since abundant structural informations are 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]

A number of peptide-derived compounds have been identified as HIV-PR inhibitors[6] but their clinical development has been hindered by their poor pharmacokinetics, including low oral bioavailability and rapid excretion,[7] and complex and expensive synthesis.[8] Therefore, in the development of nonpeptidic inhibitors of low molecular weight, some authors have recently paid attention towards seven-membered cyclic urea scaffold (**1**),[9–11] which creates 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. Further, to investigate structurally diverse class of nonpeptidic cyclic inhibitors, same authors synthesized a series of cyclic cyanoguanidines (**2**)[12] and studied their enzyme inhibition and antiviral activities. Since the development of anti-HIV chemotherapy, based on HIV-PR inhibition, will always be an ongoing need, as the virus has the ability to rapidly generate resistant mutants,[13,14] we present here a quantitative structure–activity relationship (QSAR) study on the series of both **1** and **2** to discuss in a quantitative term their relative biological merit and to provide guidelines for designing better analogues with superior pharmacokinetic and efficacy profiles.




**1**




**2**

The series of compounds subjected to QSAR studies are listed in Tables 1 and 2, where the activity parameter $IC_{90}$ is a measure of antiviral potency and refers to the molar concentration of the compound, required to reduce

Key words: Quantitative structure–activity relationship; HIV-1 protease inhibitors; cyclic cyanoguanidines; cyclic urea derivatives.
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**Table 1.** Cyclic cyanoguanidines (**2**) and their antiviral potency and HIV-1 protease inhibition activity studied by Jadhav et al.[12] and physicochemical parameters

| Compound no. | P2/P2′ | π | $I_H$ | $I_a$ | $I_e$ | log (1/IC$_{90}$) | | log (1/$K_i$) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Observed | Calcd eq (1) | Observed | Calcd eq (2) |
| **1** | H | 0.00 | 1 | 0 | 0 | —[a] | 3.62 | —[b] | 7.05 |
| **2** | Allyl | 1.00 | 0 | 0 | 0 | 4.29 | 4.29 | 7.43 | 7.12 |
| **3** | *n*-Propyl | 1.71 | 0 | 0 | 0 | 5.13 | 5.41 | 7.85 | 7.94 |
| **4** | *n*-Butyl | 2.24 | 0 | 0 | 0 | 5.59 | 5.85 | 8.56 | 8.32 |
| **5** | 3,3-Dimethylallyl | 2.15 | 0 | 0 | 0 | 5.33 | 5.80 | 7.52 | 8.27 |
| **6** | 3-Methylbutyl | 2.64 | 0 | 0 | 0 | 5.96 | 5.96 | 8.42 | 8.47 |
| **7** | Cyclopropylmethyl | 1.63 | 0 | 0 | 0 | 5.30 | 5.31 | 7.66 | 7.87 |
| **8** | Cyclobutylmethyl | 2.18 | 0 | 0 | 0 | 6.08 | 5.82 | 8.70 | 8.28 |
| **9** | Cyclopentylmethyl | 2.74 | 0 | 0 | 0 | 6.46 | 5.96 | 8.82 | 8.48 |
| **10** | Cyclohexylmethyl | 3.31 | 0 | 0 | 0 | 5.96 | 5.71 | 8.24 | 8.46 |
| **11** | Benzyl | 2.27 | 0 | 1 | 0 | 5.42 | 5.30 | 7.70 | 7.51 |
| **12** | 3-Nitrobenzyl | 2.02 | 0 | 1 | 0 | 4.75 | 5.14 | 7.05 | 7.36 |
| **13** | 4-Nitrobenzyl | 2.02 | 0 | 1 | 0 | 4.71 | 5.14 | 7.17 | 7.36 |
| **14** | 3-Aminobenzyl | 1.05 | 1 | 1 | 0 | 6.30 | 5.78 | 8.13 | 8.06 |
| **15** | 4-Aminobenzyl | 1.05 | 1 | 1 | 0 | 5.64 | 5.78 | 7.60 | 8.06 |
| **16** | 3-Cyanobenzyl | 1.71 | 0 | 1 | 0 | 5.51 | 4.85 | 7.59 | 7.12 |
| **17** | 4-Cyanobenzyl | 1.71 | 0 | 1 | 0 | 5.11 | 4.85 | 6.89 | 7.12 |
| **18** | 3-Hydroxybenzyl | 1.61 | 1 | 1 | 0 | 6.89 | 6.68 | 9.14 | 8.72 |
| **19** | 4-Hydroxybenzyl | 1.61 | 1 | 1 | 0 | 6.60 | 6.68 | 8.58 | 8.72 |
| **20** | 3-(Benzyloxy)benzyl | 3.96 | 0 | 1 | 1 | —[a] | 4.38 | 5.86 | 5.96 |
| **21** | 4-(Benzyloxy)benzyl | 3.96 | 0 | 1 | 1 | 4.17 | 4.38 | 6.05 | 5.96 |
| **22** | 3-(Hydroxymethyl)benzyl | 1.24 | 1 | 1 | 0 | 6.23 | 6.12 | 8.77 | 8.31 |
| **23** | 4-(Hydroxymethyl)benzyl | 1.24 | 1 | 1 | 0 | 5.49 | 6.12 | 7.96 | 8.31 |
| 24 | 2-Napthylmethyl | 3.45 | 0 | 1 | 0 | —[a] | 5.02 | 7.66 | 7.59 |

[a] Not used in the derivation of eq (1).
[b] Not used in the derivation of eq (2).

**Table 2.** Cyclic urea derivatives (**1**) and their antiviral potency and HIV-1 protease inhibition activity studied by Jadhav et al.[12] and physicochemical parameters

| Compound no. | P2/P2′ | π | $I_H$ | $I_a$ | $I_e$ | log (1/IC$_{90}$) | | log (1/$K_i$) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Observed | Calcd eq (3) | Observed | Calcd eq (4) |
| **1** | H | 0.00 | 1 | 0 | 0 | —[a] | 5.74 | 6.57 | 6.88 |
| **2** | Allyl | 1.00 | 0 | 0 | 0 | 5.33 | 5.21 | 8.28 | 7.54 |
| **3** | *n*-Propyl | 1.71 | 0 | 0 | 0 | 4.27[a] | 5.68 | 8.10 | 8.34 |
| **4** | *n*-Butyl | 2.24 | 0 | 0 | 0 | 6.16 | 5.81 | 8.85 | 8.48 |
| **5** | 3,3-Dimethylallyl | 2.15 | 0 | 0 | 0 | 6.07 | 5.80 | 8.80 | 8.48 |
| **6** | 3-Methylbutyl | 2.64 | 0 | 0 | 0 | 5.37 | 5.78 | 7.92 | 8.33 |
| **7** | Cyclopropylmethyl | 1.63 | 0 | 0 | 0 | 5.74 | 5.64 | 8.68 | 8.28 |
| **8** | Cyclobutylmethyl | 2.18 | 0 | 0 | 0 | 6.00 | 5.81 | 8.89 | 8.48 |
| **9** | Cyclopentylmethyl | 2.74 | 0 | 0 | 0 | 5.77 | 5.75 | 8.37 | 8.26 |
| **10** | Cyclohexylmethyl | 3.31 | 0 | 0 | 0 | 4.02[a] | 5.49 | 7.43 | 7.59 |
| **11** | Benzyl | 2.27 | 0 | 1 | 0 | 6.08 | 5.81 | 8.52 | 8.49 |
| **12** | 3-Nitrobenzyl | 2.02 | 0 | 1 | 0 | 6.01 | 5.78 | 8.55 | 8.47 |
| **13** | 4-Nitrobenzyl | 2.02 | 0 | 1 | 0 | 5.08 | 5.78 | 7.49 | 8.47 |
| **14** | 3-Aminobenzyl | 1.05 | 1 | 1 | 0 | 6.89 | 7.03 | 9.55 | 9.26 |
| **15** | 4-Aminobenzyl | 1.05 | 1 | 1 | 0 | 6.96 | 7.03 | 8.96 | 9.26 |
| **16** | 3-Cyanobenzyl | 1.71 | 0 | 1 | 0 | 5.66 | 5.68 | 8.52 | 8.34 |
| **17** | 4-Cyanobenzyl | 1.71 | 0 | 1 | 0 | 5.24 | 5.68 | 7.28 | 8.34 |
| **18** | 3-Hydroxybenzyl | 1.61 | 1 | 1 | 0 | 7.27 | 7.42 | 9.92 | 9.90 |
| **19** | 4-Hydroxybenzyl | 1.61 | 1 | 1 | 0 | 7.49 | 7.42 | 9.92 | 9.90 |
| **20** | 3-(Benzyloxy)benzyl | 3.96 | 0 | 1 | 1 | —[a] | 4.92 | 6.47 | 6.28 |
| **21** | 4-(Benzyloxy)benzyl | 3.96 | 0 | 1 | 1 | —[a] | 4.92 | 6.27 | 6.28 |
| **22** | 3-(Hydroxymethyl)benzyl | 1.24 | 1 | 1 | 0 | 7.42 | 7.19 | 9.85 | 9.52 |
| **23** | 4-(Hydroxymethyl)benzyl | 1.24 | 1 | 1 | 0 | 7.42 | 7.19 | 9.85 | 9.52 |
| 24 | 2-Napthylmethyl | 3.45 | 0 | 1 | 0 | 5.41 | 5.38 | 9.51[b] | 7.35 |

[a] Not used in the derivation of eq (3).
[b] Not used in the derivation of eq (4).

the concentration of HIV viral RNA by 90% from the level measured in an infected culture, and $K_i$ is the enzyme inhibition constant.

## Results and Discussion

The antiviral potency of the compounds of Table 1 (cyclic cyanoguanidines) was found to have a very good parabolic correlation with hydrophobic constant π of P2/P2′ substituents of the compounds and with two indicator parameters $I_H$ and $I_a$ (eq (1)).

$$\log(1/IC_{90}) = 3.219(\pm1.411)\pi - 0.604(\pm0.280)\pi^2 + 1.954(\pm0.600)I_H - 0.565(\pm0.438)I_a + 1.670$$
$$n = 21,\ r = 0.88,\ s = 0.35,\ F_{4,16} = 13.68(4.77),\ \pi_o = 2.66 \quad (1)$$

The indicator parameter $I_H$ has been used with a value of unity for a P2/P2′ substituent containing OH/$NH_2$ group, and $I_a$ has been used with a value of unity for an aromatic P2/P2′ substituent. In the equation, $n$ 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 data within the parentheses preceding the variables are 95% confidence intervals. The value of $F$ given in the parenthesis is of 99% level. The $\pi_o$ refers to the optimum value of π.

A similar correlation with an additional parameter $I_e$ was obtained for enzyme inhibition activity of these compounds (eq (2)).

$$\log(1/K_i) = 2.124(\pm1.609)\pi - 0.359(\pm0.348)\pi^2 + 1.694(\pm0.574)I_H - 0.824(\pm0.411)I_a - 1.367(\pm1.214)I_e + 5.357$$
$$n = 23,\ r = 0.92,\ s = 0.32,\ F_{5,16} = 19.28(4.44),\ \pi_o = 2.96 \quad (2)$$

$I_e$ is equal to 1 for a P2/P2′ substituent containing an ethereal moiety (C–O–C) and zero for others. The negative coefficient of it suggests that such a substituent would not be favourable to the enzyme inhibition activity of these compounds. Similarly, the negative coefficient $I_a$ in both eqs (1) and (2) indicates that the presence of an aromatic substituent would be detrimental to both antiviral and enzyme inhibition activities of these compounds. Since the correlation is parabolic with hydrophobic constant π, the receptor site may have the limited bulk tolerance, as unlike in in vivo, there is no membrane-like lipid-water barrier in the in vitro system to optimize the lipophilic effect. Thus, eqs (1) and (2) suggest that both the antiviral potency and the enzyme inhibition activity of cyclic cyanoguanidines are governed by the hydrophobic property of the P2/P2′ substituents with an optimal value of π equal to 2.66 and 2.96, respectively, which are essentially the same. However, in both the cases the positive coefficient of $I_H$ suggests that an −OH or $-NH_2$ containing substituent would be more beneficial than any other substituent. This is probably because OH or $NH_2$ moiety may form the hydrogen bond with the receptor.

In deriving eq (1) compounds **1**, **20**, and **24**, and in deriving eq (2) compound **1** were not included because the corresponding activity data for them are not reported. Equation (1), however, predicts the antiviral potency of **1**, **20** and **24** as 3.62, 4.38 and 5.02, respectively, and eq (2) predicts enzyme inhibition activity of **1** as 7.05.

In the case of cyclic urea derivatives (Table 2), too, both antiviral potency and enzyme inhibition activity of the compounds were found to be significantly correlated with the hydrophobic property of the substituents and indicator variable $I_H$ (eqs (3) and (4)).

$$\log(1/IC_{90}) = 1.587(\pm1.366)\pi - 0.340(\pm0.307)\pi^2 + 1.780(\pm0.428)I_H + 3.962$$
$$n = 19,\ r = 0.94,\ s = 0.27,\ F_{3,15} = 37.53(5.42),\ \pi_o = 2.33 \quad (3)$$

$$\log(1/K_i) = 2.986(\pm0.870)\pi - 0.688(0.175)\pi^2 + 1.637(\pm0.581)I_H + 5.241$$
$$n = 23,\ r = 0.92,\ s = 0.42,\ F_{3,19} = 34.49(5.01),\ \pi_o = 2.17 \quad (4)$$

In deriving eq (3), compounds **1**, **20** and **21** were not included because their activity data are not reported. Equation (3), however, predicts their activities as 5.74, 4.92 and 4.92, respectively. Compounds **3** and **10** were also not included, as they exhibited an aberrant behaviour. The activities of these compounds as predicted by eq (3) were much higher than their corresponding observed values (5.68 versus 4.27 and 5.49 versus 4.02, respectively). The reason for the low observed activities of these compounds may be due to some steric effects produced by the substituents, or misorientation of the substituents towards the active site of the receptor.

Also in deriving eq (4) compound **24** has not been included, as it behaves as an outlier. Its predicted activity value (7.35) is quite low as compared to its observed activity (9.51). The high observed activity may be due to a very good π-stacking interaction of β-naphthyl moiety with S2, S2′ pockets of the enzyme.

Now it is to be noted that in both the series the P2/P2′ substituents are the same, but if we compare eqs (1) and (2) with eqs (3) and (4) correspondingly, we find that aromatic substituents in cyclic cyanoguanidine series produce an adverse effect on both antiviral potency as well as enzyme inhibition activity but not in cyclic urea series. Further, an ethereal moiety in the substituent has an additional negative effect on the enzyme inhibition activity of cyclic cyanoguanidines.

Such an effect of an ethereal moiety on the enzyme inhibition activity of cyclic ureas was, however, also

observed when a large series of these compounds, studied by the same group of authors[11] who reported the compounds of Table 2, were subjected to QSAR.[15] In that series, a few of the compounds of Table 2 (**2**–**12** and **24**) were common, but the correlation obtained was:

$$\log(1/K_i) = 2.751(\pm0.771)\pi - 0.606(\pm0.166)\pi^2 + 1.766(\pm0.486)I_H - 1.251(\pm0.603)I_o - 1.680(\pm0.436)I_e + 5.400$$
$$n = 48,\ r = 0.93,\ s = 0.46,\ F_{5,42} = 51.78(3.49),\ \pi_o = 2.27 \quad (5)$$

The absence of parameter $I_e$ in eq (4) may be due to the facts that there are only two compounds (**20** and **21**) in the series (Table 2) for which $I_e = 1$ and both the compounds have very low activity which can be attributed to a more dominant factor than an ethereal moiety. It may be that the bulky (benzyloxy)benzyl substituent in these compounds produces a dominant steric effect, leaving no scope for the ethereal moiety to play any role. The negative effect of the ethereal moiety (C–O–C fraction), whatsoever, can be assumed to be due to the repulsion between the electron pairs at its oxygen and an anionic site at the receptor. Compounds **20** and **21** of Table 2 were not present in the earlier series for which eq (5) was obtained.

The additional parameter $I_o$ in eq (5) stands for an aromatic P2/P2′ substituent bearing an ortho group. No such substituents are present in the present series (Table 2), hence $I_o$ did not appear in eq (4). An ortho group may create some steric hindrance in the interaction of the molecule with the receptor, hence the negative effect.

Leaving $I_e$ and $I_o$ parameters apart, there seems an excellent similarity between eqs (4) and (5) with respect to the coefficients of variables as well as the values of statistical parameters $r$, $s$ and $\pi_o$. This similarity between two equations, where eq (4) has been obtained for a smaller group and eq (5) relatively for a larger group, shows the validity of the correlation.

In our previous study, an ortho group was found to affect the antiviral potency also (eq (6)). Since there are no aromatic P2/P2′ substituents bearing an ortho group in the present case, the parameter $I_o$ did not appear in eq (3). Otherwise, eqs (3) and (6) are also quite similar and equally significant, validating the correlation for antiviral potency, too.

$$\log(1/IC_{90}) = 2.732(\pm0.759)\pi - 0.592(\pm0.180)\pi^2 + 1.914(\pm0.357)I_H - 0.810(\pm0.414)I_o + 2.705$$
$$n = 39,\ r = 0.93,\ s = 0.33,\ F_{4,34} = 50.80(3.93),\ \pi_o = 2.31 \quad (6)$$

To make a comparative study of the activities of cyanoguanidines and cyclic urea derivatives, compounds of Tables 1 and 2 were merged and eqs (7) and (8) were obtained for the combine, where the parameter $I_g$ is equal to one for cyclic cyanoguanidines and zero for cyclic urea derivatives. The negative coefficient of $I_g$ in both eqs (7) and (8) indicates that cyclic cyanoguanidines would be less active than cyclic urea derivatives both as an antiviral and as a PR-inhibitor. In deriving eqs (7) and (8), all those compounds were excluded which were not taken in the derivation of eqs (1) and (3) (for antiviral potency) and eqs (2) and (4) (for enzyme inhibition activity).

$$\log(1/IC_{90}) = 2.416(\pm1.139)\pi - 0.474(\pm0.236)\pi^2 + 1.696(\pm0.411)I_H - 0.532(\pm0.282)I_g + 2.957$$
$$n = 40,\ r = 0.861,\ s = 0.41,\ F_{4,35} = 25.12(3.95) \quad (7)$$

$$\log(1/K_i) = 2.942(\pm0.878)\pi - 0.646(\pm0.171)\pi^2 + 1.392(\pm0.491)I_H - 0.625(\pm0.332)I_g + 5.208$$
$$n = 46,\ r = 0.847,\ s = 0.53,\ F_{4,41} = 26.07(3.82) \quad (8)$$

The comparison of X-ray crystal structures of cyclic cyanoguanidines with those of cyclic urea derivatives reveal that there is an almost perfect overlapping between the seven membered rings of cyclic cyanoguanidines and cyclic urea derivatives except some difference in the orientation of their P2/P2′ substituents.[12] This difference in the orientation of their P2/P2′ substituents may be due to the steric interaction in cyclic cyanoguanidines of the methylene moiety with the cyano group, which is rotated out of the plane formed by the −N−C≡N atoms. As in cyclic urea derivatives, the structural water molecule is displaced by the exocyclic nitrogen of the cyclic cyanoguanidines, but the cyano group present on the exocyclic nitrogen causes movement of one of the flaps of the enzyme from the active site which presumably results in the enlargement of the S2 pocket of the enzyme.[12] Therefore, in cyclic cyanoguanidines, large alkyl groups in P2 can be more readily accommodated in the active site. Our theoretical study also confirms this, but more potent cyclic cyanoguanidines may be obtained with large alkyl group with an optimum π value of 2.66 for antiviral potency and 2.96 for enzyme inhibition activity. A hydrogen bond forming group, like OH or $NH_2$, will have an added advantage. A schematic representation of the bindings of substituents with the enzyme is shown in Figure 1, where a P2 substituent projects into the S2 pocket of the enzyme for hydrophobic interaction and P1/P1′ substituents into S1/S1′ pockets, most probably for dispersion interaction as in cyclic urea derivatives.[15] Since P2′ substituents in cyclic cyanoguanidines are not assumed to interact with the enzyme, it may be the reason for these compounds to be less active than cyclic urea derivatives where both P2/P2′ substituents are assumed to interact with the enzyme.[15]

As resistant variants may emerge more quickly against symmetric inhibitors,[16] asymmetric cyclic urea derivatives may have better affinity with higher efficacy than cyclic cyanoguanidines.

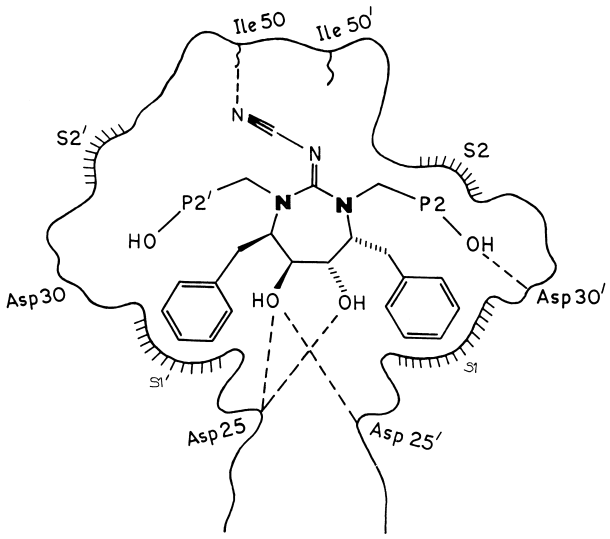


**Figure 1.** A proposed model for the interaction of cyclic cyanoguanidines with HIV-1 protease.

## Conclusion

An overall conclusion that can be drawn from the present study is that both antiviral and enzyme inhibition activities of cyclic cyanoguanidines as well as cyclic ureas are the function of hydrophobic property of P2/P2′ substituents. These substituents can be of further advantage if they contain OH- or $NH_2$- like hydrogen bond donor groups. However, a cyclic urea derivative is found to have better antiviral potency or PR-inhibition acivity than corresponding cyclic cyanoguanidine derivative. This difference is assumed to be due to the binding of both P2 and P2′ substituents in cyclic ureas with the receptor, whereas in cyanoguanidines only P2 substituent is assumed to bind. Also an aromatic P2/P2′ substituent appears to have an adverse effect on the activities of cyanoguanidines.

## Experimental

All the compounds of Tables 1 and 2 used in QSAR analysis were those synthesized and screened by Jadhava et al.,[12] where the inhibition of HIV-1 protease was measured by assaying the cleavage of a fluorescent peptide substrate using high performance liquid chromatography and the antiviral potency was assayed by measuring the effect of the compounds on the accumulation of viral RNA transcripts 3 days after infection of MT-2 cells with HIV-1 RF.

The physicochemical parameter—hydrophobic constant π—has been calculated as suggested by Hansch and Leo[17] and the correlations have been obtained using a self-developed software of least-square method.

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