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A Quantitative Structure–Activity Relationship Study on Some Sulfolanes and Arylthiomethanes Acting as HIV-1 Protease Inhibitors

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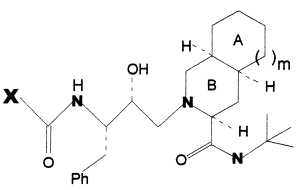
Abstract—A quantitative structure–activity relationship (QSAR) study on some sulfolanes and arylthiomethanes acting as human immunodeficiency virus-1 (HIV-1) protease inhibitors reveals that in the case of sulfolanes an octahydropyrindene ring and a five-membered 3(*S*)-sulfolane ring with a hydrophobic 2-substituent (cis to 3-substituent) will be crucial for the inhibition activity. The binding of a sulfolane, which is a nonpeptidic molecule, with the enzyme is shown to partly mimic the binding of a peptidic inhibitor. The 2-substituent is found to have strong hydrophobic interaction with the receptor. Similarly, in the case of arylthiomethanes, one of the substituents of the methane is found to have strong hydrophobic interaction with the enzyme, while the aryl substituent (4-hydroxy-6-phenyl-2-oxo-2H-pyran-3-yl) is assumed to be involved in the hydrogen bondings.

Introduction

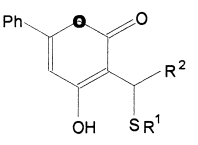
The human immunodeficiency virus (HIV) is a pathogenic retrovirus and causative agent for acquired immunodeficiency syndrome (AIDS) and its related disorders. A homodimeric aspartyl protease is found to be essential for the maturation of HIV-1, the most common and prevalent form of the virus.[1] Therefore, the inhibition of this protease (HIV-1-PR) in vitro results in the production of progeny virions, which are immature and noninfectious.[2,3] Consequently, the study of the inhibition of this enzyme has drawn the considerable interest of medicinal chemists for the development of AIDS chemotherapy. Since the structure of HIV-1-PR is well studied, it has become an attractive target for computer-aided drug design strategies.[4,5]

A number of peptide-derived compounds have been identified as HIV-1-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, attention has been focussed to investigate nonpeptide inhibitors of low molecular weight. Further, since HIV mutates at the level of protease to render resistance to antiviral drugs, targetting the enzyme,[9] there is a marked interest in developing structurally diverse and/or small molecule leads which interact with a limited number of binding sites critical for HIV-1-PR inhibition. This study can be very fruitfully facilitated by a quantitative structure–activity relationship (QSAR) study which investigates the physicochemical and structural properties of molecules that can lead them to strongly bind with the receptors.

Thus in search of small nonpeptidic HIV-1-PR inhibitors, Ghosh et al.[10] synthesized a series of sulfolanes (**1**) and Vara Prasad et al.[11] a series of (4-hydroxy-6-phenyl-2-oxo-2H-pyran-3-yl)thiomethanes (**2**) and studied their inhibition activity. The present communication reports a QSAR study on those two series of HIV-1-PR inhibitors.



1



2

Key words: Quantitative structure–activity relationship; HIV-1 protease inhibitors; sulfolanes; arylthiomethanes.
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Materials and Methods

The series of sulfolanes studied by Ghosh et al.[10] is listed in Table 1 and the series of thiomethanes studied by Vara Prasad et al.[11] in Table 2. In both the tables, the IC_{50} refers to the molar concentration of the compound leading to 50% inhibition of the enzyme activity.

A Hansch approach has been adopted for QSAR study. The hydrophobic constant π and the van der Waals volume V_w used in the correlations have been calculated as suggested by Hansch and Leo[12] and Moriguchi et al.,[13] respectively.

Results and Discussion

The inhibition activity of compounds of Table 1 was found to have a good parabolic correlation with the hydrophobic constant π of 2-substituent in the X group of the compounds (eq (1)). In eq (1), 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 observed and calculated activities, and the data within the parentheses are 95% confidence intervals.

$$\log(1/IC_{50}) = 2.130(\pm0.901)\pi_2 - 0.793(\pm0.460)\pi_2^2 + 6.699$$
$$n = 33,\ r = 0.775,\ s = 0.48,\ F_{2,30} = 22.49\ (3.32) \quad (1)$$

The F-value given in parentheses is of 99% level. This equation accounts for 60% of the variance in the activity ($r^2 = 0.60$) and thus the hydrophobic property of 2-substituents seems to play a major role in the inhibition potency of the compounds.

The correlation was found to be significantly improved when some indicators variables were used. A variable I_m was used to account for the effect of size of A ring. It was given a value of 1 for a five-membered ring ($m = 0$) and zero for a six-membered ring ($m = 1$). Another variable I_5 was used for a five-membered sulfolane ring in X-substituent. For such a ring it was given a value of 1 and for others 0. A third variable I_6 equal to 1 was defined for a six-membered ring in X-substituent. For others it was taken equal to zero. A fourth variable $I_s = 1$ was taken to describe the effect of a 3(*S*) configuration of the ring in X relative to a 3(*R*) configuration. All these variables were successively found to improve the correlation, giving finally a highly significant correlation as expressed by eq (5).

$$\log(1/IC_{50}) = 2.014(\pm0.809)\pi_2 - 0.715(\pm0.415)\pi_2^2 + 0.722(\pm0.502)I_m + 6.603$$
$$n = 33,\ r = 0.832,\ s = 0.43,\ F_{3,29} = 21.72\ (4.54) \quad (2)$$

$$\log(1/IC_{50}) = 1.771(\pm0.768)\pi_2 - 0.662(\pm0.383)\pi_2^2 + 0.662(\pm0.463)I_m + 0.475(\pm0.382)I_5 + 6.395$$
$$n = 33,\ r = 0.866,\ s = 0.38,\ F_{4,28} = 21.01\ (4.07) \quad (3)$$

$$\log(1/IC_{50}) = 1.667(0.687)\pi_2 - 0.616(\pm0.342)\pi_2^2 + 0.614(\pm0.413)I_m + 0.324(\pm0.355)I_5 - 0.861(\pm0.603)I_6 + 6.581$$
$$n = 33,\ r = 0.900,\ s = 0.33,\ F_{5,27} = 23.07\ (3.79) \quad (4)$$

$$\log(1/IC_{50}) = 1.717(\pm0.594)\pi_2 - 0.634(\pm0.296)\pi_2^2 + 0.520(\pm0.362)I_m + 0.302(\pm0.307)I_5 - 0.867(\pm0.521)I_6 + 0.362(\pm0.231)I_s + 6.406$$
$$n = 33,\ r = 0.930,\ s = 0.28,\ F_{6,26} = 27.59\ (3.59) \quad (5)$$

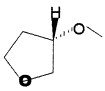
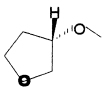
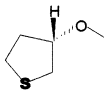
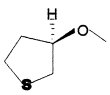
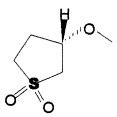
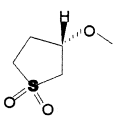
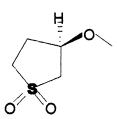
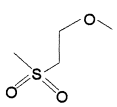
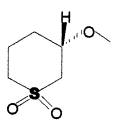
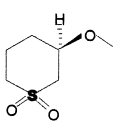
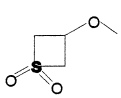
However, even in eq (5), compound **20** was found to be misfit. Equation (5) predicts very high activity for it as compared to its observed activity (Table 1). Therefore, when this compound was excluded, a further improved correlation was obtained (eq (6)), accounting for more than 90% of the variance in the activity ($r^2 = 0.904$). The exclusion of this compound makes the I_5 parameter also statistically significant at 95% confidence level, which is only marginally significant in eq (5).

$$\log(1/IC_{50}) = 1.524(\pm0.489)\pi - 0.575(\pm0.240)\pi_2^2 + 0.479(\pm0.292)I_m + 0.426(\pm0.256)I_5 - 0.893(\pm0.420)I_6 + 0.287(\pm0.190)I_s + 6.470$$
$$n = 32,\ r = 0.951,\ s = 0.23,\ F_{6,25} = 39.16\ (3.63) \quad (6)$$

The fairly low activity of **20** can be attributed to the presence in sulfolane ring of a 5-Me group in R-configuration that might produce some steric effects. This gives a structure which is exactly opposite stereoisomerically to **19**, which has a much better activity.

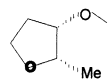
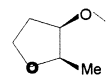
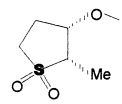
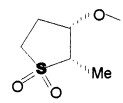
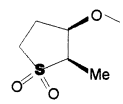
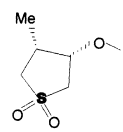
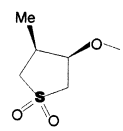
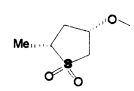
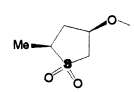
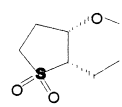
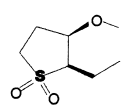
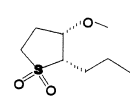
Now from eq (6), which exhibits a highly significant correlation, we can conclude that a five-membered A ring and a five-membered sulfolane ring in 3(*S*)-configuration and with a lipophilic 2-substituent (*cis* to 3-substituent) will be highly beneficial to the activity. Only a six-membered ring will have the negative effect, which is probably due to some steric effects produced by it. The potency of compounds can be controlled by the lipophilicity of the 2-substituent. The correlation has been parabolic in π_2 and the optimum value of π_2, $(\pi_2)_{opt}$, as obtained from eq (6) is 1.32, which is essentially

Table 1. The HIV-1-PR inhibition activity of some sulfolanes (**1**) and their physicochemical parameters used in the regression

Compd no.	X	m	π_2	I_5	I_6	I_m	I_s	log(1/IC_{50})		
								Observed[a]	Calculated (eq (5))	Calculated (eq (6))
1		1	0.00	0	0	0	1	6.88	6.77	6.76
2		0	0.00	0	0	1	1	7.22	7.29	7.24
3		1	0.00	0	0	0	1	6.88	6.77	6.76
4		1	0.00	0	0	0	0	6.66	6.41	6.47
5		1	0.00	1	0	0	1	7.12	7.07	7.18
6		0	0.00	1	0	1	1	7.95	7.59	7.66
7		1	0.00	1	0	0	0	6.85	6.71	6.90
8		1	0.00	0	0	0	0	5.99	6.41	6.47
9		1	0.00	0	1	0	1	5.76	5.90	5.86
10		1	0.00	0	1	0	0	5.68	5.54	5.58
11		1	0.00	0	0	0	0	6.98	6.41	6.47

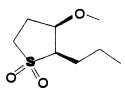
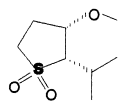
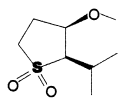
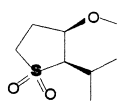
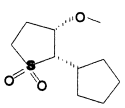
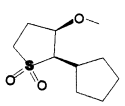
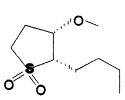
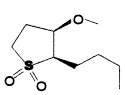
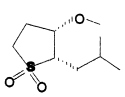
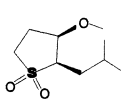
(continued)

Table 1—*contd*

Compd no.	X	m	π_2	I_5	I_6	I_m	I_s	log(1/IC_{50})		
								Observed[a]	Calculated (eq (5))	Calculated (eq (6))
12		1	0.52	0	0	0	1	7.28	7.49	7.39
13		1	0.52	0	0	0	0	6.77	7.13	7.11
14		1	0.52	1	0	0	1	7.94	7.79	7.82
15		0	0.52	1	0	1	1	7.89	8.31	8.30
16		1	0.52	1	0	0	0	7.65	7.43	7.53
17		1	0.00	1	0	0	1	7.16	7.07	7.18
18		1	0.00	1	0	0	0	6.66	6.71	6.90
19		1	0.00	1	0	0	1	7.09	7.07	7.18
20		1	0.00	1	0	0	0	5.80	6.71	6.90
21		1	1.05	1	0	0	1	8.27	8.18	8.15
22		1	1.05	1	0	0	0	7.88	7.81	7.86
23		1	1.58	1	0	0	1	8.21	8.20	8.16

(continued)

Table 1—*contd*

Compd no.	X	m	π_2	I_5	I_6	I_m	I_s	log(1/IC_{50})		
								Observed[a]	Calculated (eq (5))	Calculated (eq (6))
24		1	1.58	1	0	0	0	7.70	7.84	7.87
25		1	1.45	1	0	0	1	7.96	8.23	8.19
26		0	1.45	1	0	1	0	8.52	8.39	8.38
27		1	1.45	1	0	0	0	8.46	7.87	7.90
28		1	1.99	1	0	0	1	8.21	7.98	7.94
29		1	1.99	1	0	0	0	7.65	7.61	7.65
30		1	2.11	1	0	0	1	7.83	7.88	7.85
31		1	2.11	1	0	0	0	7.34	7.52	7.56
32		1	1.98	1	0	0	1	7.92	7.99	7.95
33		1	1.98	1	0	0	0	7.52	7.63	7.67

[a] Taken from ref. 10.

the same as can be obtained from eq (1) (1.34). Thus, a compound having 2-substituent of $\pi = 1.32$ and having all other positive factors can be the most potent compound with a predicted activity of 8.67. This compound can be obtained by changing the 2-substituent of **25** and its six-membered A ring to a five-membered one. Thus slightly a more potent compound than **26**, the most potent compound listed in Table 1, can be expected.

HIV-1-PR is an aspartic protease, which is an endopeptidase. The primary sequence of an aspartic protease has two different Asp-Thr-Gly sequences and the

Table 2. The HIV-1-PR inhibition activity of some arylthiomethanes (**2**) and their physicochemical parameters used in the regression

Compd no.	R^1	R^2	π_{R2}	$V_{w,R2}$ (10^2 Å^3)	I_{R2}	I_{R1}	log(1/IC_{50})		
							Observed[a]	Calculated (eq (8))	Calculated (eq (9))
1	C_6H_5	H	0.00	0.056	0	0	4.07	4.15	4.16
2	C_6H_5	C_6H_5	1.35	0.785	0	0	6.11	6.07	6.01
3	C_6H_5	2-Naphthyl	2.52	1.205	0	0	5.11	5.33	4.95
4	C_6H_5	Cyclohexyl	2.43	0.833	0	0	5.61	5.47	5.97
5	C_6H_5	$CH_2CH(CH_3)_2$	1.77	0.707	1	0	6.39	6.66	6.57
6	C_6H_5	$CH_2CH_2CH(CH_3)_2$	2.30	0.861	1	0	6.41	6.24	6.47
7	2-Naphthyl	C_6H_5	1.35	0.785	0	0	5.61	6.07	6.01
8	$CH_2C_6H_5$	C_6H_5	1.35	0.785	0	0	6.32	6.07	6.01
9	$CH_2C_6H_5$	$CH_2CH(CH_3)_2$	1.77	0.707	1	0	6.59	6.66	6.57
10	$CH_2C_6H_5$	CH_2cyclopropyl	1.28	0.603	1	0	7.08	6.63	6.52
11	Cyclohexyl	C_6H_5	1.35	0.785	0	0	6.32	6.07	6.01
12	Cyclohexyl	$CH_2CH(CH_3)_2$	1.77	0.707	1	0	6.50	6.66	6.57
13	Cyclohexyl	CH_2cyclopropyl	1.28	0.603	1	0	6.83	6.63	6.52
14	Cyclohexyl	CH_2cyclopentyl	2.40	0.898	1	0	6.27	6.09	6.42
15	Cyclohexyl	$CH_2C(CH_3)_3$	2.17	0.861	1	0	6.52	6.39	6.47
16	Cyclohexylmethyl	$CH_2CH(CH_3)_2$	1.77	0.707	1	0	6.07	6.66	6.57
17	Cyclopentyl	Cyclopentyl	1.87	0.757	0	1	6.65	6.59	6.67
18	Cyclopentyl	$CH_2CH(CH_3)_2$	1.77	0.707	1	1	7.24	7.24	7.22
19	Cyclopentyl	CH_2cyclopropyl	1.28	0.603	1	1	7.16	7.21	7.17

[a] Taken from ref. 11.

apostructure of it shows these two chains running in opposite directions with a water molecule bound between two aspartates. This water molecule is believed to be a nucleophile for the enzyme-catalyzed amide hydrolysis of the substrate. The substrates of aspartic proteases are peptidic in nature and possess a scissile bond (Fig. 1). In substrate–enzyme interaction, this scissile bond is attacked by the water molecule of the enzyme, and a few amino acid residues of the substrate interact with corresponding binding sites at the enzyme. This interaction is stabilized by several hydrogen bondings between the backbones of the substrate and the enzyme.[4,14]

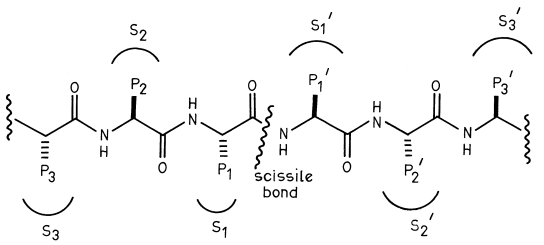


Figure 1. A peptidic substrate of aspartic proteases. The $P_1,P_2,\ldots P_n$ and $P_1',P_2',\ldots P_n'$ are the aminoacid residues, and $S_1,S_2,\ldots S_n$ and $S_1',S_2',\ldots S_n'$ are the corresponding binding sites at the enzyme. These nomenclatures are according to Schechter and Burger.[15]

The discovery of substrate mimicking HIV-1-PR inhibitors was based on the synthesis of substrate analogues in which the scissile bond was replaced by a noncleavable isostere with tetrahedral geometry that could mimic the tetrahedral transition state of the proteolytic reaction. Thus, several inhibitors with hydroxyethylene or hydroxyethylamine isostere replacement were prepared, which could bind with the enzyme as shown in Figure 2. In the inhibitor–enzyme interaction, the enzyme's water molecule makes hydrogen bonds with both the inhibitor and the enzyme with approximately tetrahedral geometry. This water molecule in the complex is known as 'flap' water. A sulfolane can bind with this flap water as shown in Figure 3, which also exhibits how other portions of the inhibitor can interact with the enzyme leading to its inhibition. The sulfone oxygens can have the hydrogen bondings with Asp 29 and Asp 30 present in S_2 binding domain of the HIV-1 protease, and the hydrophobic 2-substituent can have the hydrophobic interaction with a hydrophobic cavity present in the S_2 region.

In the case of arylthiomethanes (Table 2), too, the hydrophobic nature of substituents is found to play a major role. A significant parabolic correlation is obtained between the enzyme inhibition activity of the compounds and the hydrophobic parameter of R^2-substituents (eq (7)), suggesting that these substituents may be involved in strong hydrophobic interaction with the enzyme.

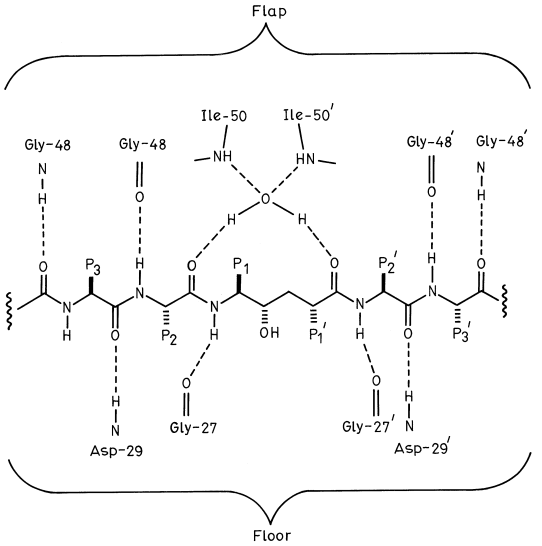


Figure 2. A model of binding of a substrate-based HIV-1-PR inhibitor with the receptor.[14]

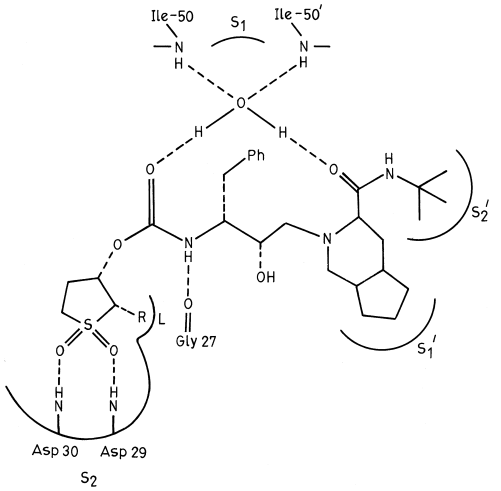


Figure 3. A model proposed for the binding of a sulfolane with HIV-1-PR. S_1',S_2' can be the hydrophobic sites in the enzyme. S_2 site is shown to participate in the hydrogen bondings but also to contain a small hydrophobic cavity L which can accommodate the hydrophobic 2-substituent.

$$\log(1/IC_{50}) = 3.263(\pm1.247)\pi_{R2} - 1.042(\pm0.418)(\pi_{R2})^2 + 4.048$$
$$n = 19,\ r = 0.811,\ s = 0.43,\ F_{2,16} = 15.39\ (6.23) \quad (7)$$

However, since the correlation is parabolic, the receptor site may have the limited bulk tolerance, as unlike in in vivo there is no membrane-like lipid–water barrier in in vitro system to optimize the lipophilic effect. The optimum value of π_{R2} as obtained from eq (7) is 1.57, suggesting that only a moderately lipophilic or essentially only a moderately bulky R^2-substituent can be advantageous.

The correlation expressed by eq (7) was found to be further improved significantly when two indicator variables were introduced (eq (8)). A variable $I_{R2} = 1$ was used for all those R^2-substituents which were attached to C-3α through CH_2 bridge group and the other variable $I_{R1} = 1$ was used for a cyclopentyl group in R^1-substituents.

$$\log(1/IC_{50}) = 2.516(\pm0.844)\pi_{R2} - 0.813(\pm0.279)(\pi_{R2})^2 + 0.591(\pm0.309)I_{R2} + 0.586(\pm0.403)I_{R1} + 4.150$$
$$n = 19,\ r = 0.940,\ s = 0.25,\ F_{4,14} = 26.67\ (5.03),\ (\pi_{R2})_{opt} = 1.55 \quad (8)$$

The statistically quite significant positive coefficients of these variables indicate that such substituents, for which these variables stand, are crucial for the activity. In R^2-substituent, a CH_2 bridge can provide conformational flexibility to the substituent, because of which the substituent may be able to have the desired hydrophobic interaction with the receptor site. The advantageous role of cyclopentyl group in R^1-substituents can be assumed to be due to its ability to make a complete steric fit with the receptor site.

The use of van der Waals volume (V_w) in place of π for R^2-substituents gave equally significant correlation (eq (9)), supporting the suggestion that very bulky R^2-substituent will not be tolerated at the receptor site. However, there exists a very good correlation between $V_{w,R2}$ and π_{R2} ($r = 0.865$), hence it is difficult to say whether it is the hydrophobic interaction or the dispersion interaction which really takes place between the R^2-substituent and the receptor.

$$\log(1/IC_{50}) = 6.238(\pm2.186)V_{w,R2} - 4.404(\pm1.726)(V_{w,R2})^2 + 0.535(\pm0.330)I_{R2} + 0.644(\pm0.415)I_{R1} + 3.828$$
$$n = 19,\ r = 0.937,\ s = 0.26,\ F_{4,14} = 25.16\ (5.03),\ (V_{w,R2})_{opt} = 0.708 \quad (9)$$

Since it has been observed that protease has four hydrophobic pockets near its active site and that the favourable hydrophobic interactions with these pockets are desirable for an inhibitor to achieve nanomolar potency,[16] it is plausible to assume, in the present case, that it is only the hydrophobic interaction which is responsible for the binding of the R^2-substituent, and

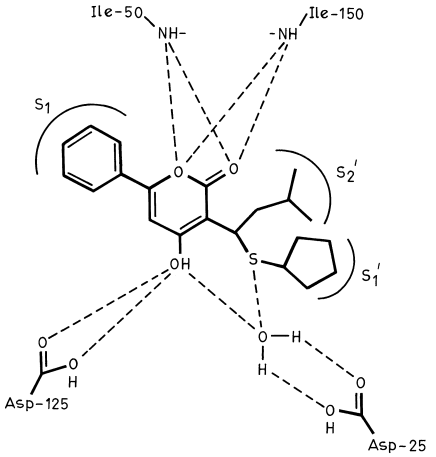


Figure 4. A model of binding of arylthiomethanes with HIV-1-PR based on X-ray crystallographic studies.[11] S_1,S_1',S_2' all can be hydrophobic sites.

Table 3. Mutual correlations (r-values) among the variables used in eqs (6) and (8)

eq (6)					
	π_2	I_m	I_5	I_6	I_s
π_2	1.00	0.126	0.548	0.243	0.095
I_m		1.00	0.051	0.098	0.166
I_5			1.00	0.383	0.042
I_6				1.00	0.016
I_s					1.00
eq (8)					
	π_{R2}	I_{R2}	I_{R1}		
π_{R2}	1.00	0.297	0.025		
I_{R2}		1.00	0.208		
I_{R1}			1.00		

even the R^1-substituent, with the enzyme. Wang et al.[17] also observed that at least two additional factors are important in the binding of a compound to HIV-1 protease. The first is the conformational flexibility of the inhibitor molecule and the second is the hydrophobic interactions between an inhibitor and the enzyme. We have also discussed recently that most of the protease inhibitors involve hydrophobic interactions.[18] According to Vara Prasad et al.[11] the R^1- and R^2-substituents interact with S_1' and S_2' sites of the enzyme (Fig. 4). Our theoretical study fully conforms to it and predicts the same compound **18** (Table 2) to possess the highest activity as the one observed by experiment.

The independent variables used in the two pertinent equations, eqs (6) and (8), finally obtained for Tables 1 and 2, respectively, were found to have no mutual correlations (Table 3).

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