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QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIPS OF SOME HIV-PROTEASE INHIBITORS

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A quantitative structure–activity relationship (QSAR) study has been made on different series of cycloalkylpyranones acting as human-immunodeficiency-virus type 1 (HIV-1) protease inhibitors. The results suggest that the enzyme binding affinity of the compounds would be favoured by a cyclooctyl ring, a 3-cyclopropylphenylmethyl substituent at the pyranone ring, and a 4-CN-2-pyridine-, an N-Me-imidazole-, or a 3- or 4-CN-phenyl-sulfonamide group at the meta position of the phenyl ring of the 3-substituent.

Keywords: Quantitative structure–activity relationship; HIV-1 protease inhibitors; Cycloalkylpyranones

INTRODUCTION

The inhibition of human-immunodeficiency-virus (HIV) protease, a homodimeric aspartyl protease which is essential for viral maturation,[1] has attracted considerable interest from the medicinal chemists for the development of acquired immunodeficiency syndrome (AIDS) therapy. The HIV, particularly HIV-1, the most common form of the virus, is a pathogenic retrovirus and causative agent of AIDS. The inhibition of HIV-1-Protease (HIV-1-PR) *in vitro* results in the production of progeny virions, which are immature and noninfectious.[2,3] Since the structure of this enzyme has been well studied, it has become an attractive target for computer-aided drug design strategies.[4,5]

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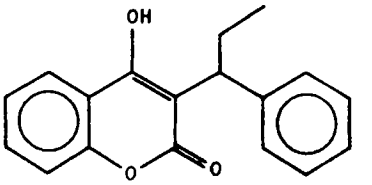
A number of peptide-derived compounds have been identified as HIV-1-PR inhibitors[6] but their clinical development has been hindered by their poor pharmacokinetics, including low oral bioavailability and rapid excretion,[7] and complex and expensive synthesis.[8] Therefore, attention was focussed on investigating nonpeptidic inhibitors of low molecular weight, resulting within a short time in the identification of a lead structure, 4-hydroxy coumarin (**1**).[9] This lead structure led to the development of several series of cycloalkylpyranones (**2**),[10–13] which exhibited better enzyme



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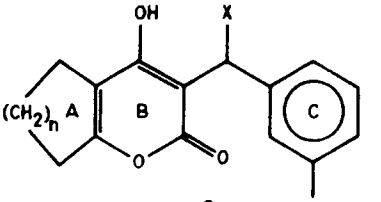

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inhibition activity than (**1**). For the development of still better analogues, *it* is essential to perform a quantitative structure–activity relationship (QSAR) study on this class of protease inhibitors. The QSAR will lead to assessment of the specific effects of various kinds of substituents and modifications in the lead structure and thus reducing trial-and-error factors. Since the virus has the ability to rapidly generate resistant mutants,[14,15] the development of anti-HIV chemotherapy based on HIV-PR inhibition will always be an ongoing need.

MATERIALS AND METHOD

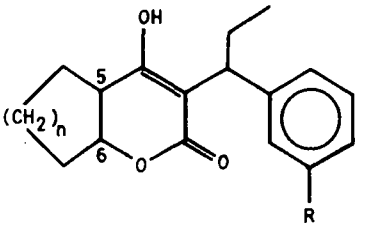
All the cycloalkylpyranones series listed in Tables I–VI and their HIV-1-PR binding affinity (K_i) data have been taken from the reports of Romines *et al.*[11–13] The analysis on this data has been performed using either the

simple parametric method developed by Hansch[16] or a nonparametric method developed by Fujita and Ban,[17] and a simple least square method [18] has been applied to obtain the results.

RESULTS AND DISCUSSION

The cycloalkylhydropyrones listed here have been studied[12] for the effects on their activity of changes in the size of the alkyl ring A and of the various modifications in the substituent at the 3-position. In Table I, compounds do not have much variations in the 3-position substituents, but vary in the size of the alkyl ring from 5-membered to 8-membered with saturation or

TABLE I Cycloalkylpyranones studied by Romines *et al.*[12] and their HIV-1-PR binding affinity



Compound no.	*R*	*Saturated/ unsaturated at 5–6*	*n*	I_1	I_2	I_3	log(1/K_i)	
							Observed	*Calculated Eq.* (1)
1	H	Unsaturated	1	0	1	0	6.16	6.24
2	H	Unsaturated	2	0	1	0	5.96	6.24
3	H	Unsaturated	3	0	1	0	6.32	6.24
4	H	Unsaturated	4	1	1	0	7.13	6.78
5	H	Unsaturated	6	0	1	0	—	6.24
6	$NHSO_2$–C_5H_5N–CN	Unsaturated	1	0	1	1	10.13	10.27
7	$NHSO_2$–C_5H_5N–CN	Unsaturated	2	0	1	1	10.19	10.27
8	$NHSO_2$–C_5H_5N–CN	Unsaturated	3	0	1	1	10.74	10.27
9	$NHSO_2$–C_5H_5N–CN	Unsaturated	4	1	1	1	11.16	10.82
10	$NHSO_2$–C_5H_5N–CN	Unsaturated	6	0	1	1	9.60	10.27
11	H	Saturated	1	0	0	0	—	5.81
12	H	Saturated	2	0	0	0	6.17	5.81
13	H	Saturated	3	0	0	0	—	5.81
14	H	Saturated	4	1	0	0	5.92	6.36
15	$NHSO_2$–C_5H_5N–CN	Saturated	1	0	0	1	9.83	9.84
16	$NHSO_2$ C_5H_5N–CN	Saturated	2	0	0	1	10.30	9.84
17	$NHSO_2$–C_5H_5N–CN	Saturated	3	0	0	1	9.72	9.84
18	$NHSO_2$ C_5H_5N–CN	Saturated	4	1	0	1	10.13	10.39

unsaturation of the 5,6-bond. The effects of these changes could be easily specified by using only indicator variables I_1, I_2, and I_3 with a value of 1 each for $n=4$, unsaturation of the 5,6-bond, and $R=$4-cyano-2-pyridinesulfonamide, respectively. From the excellent correlation obtained (Eq. (1)), the maximum weight was found to be attached with I_3 variable, signifying a predominant role of 4-cyano-2-pyridinesulfonamide group at the meta position (3′) of the phenyl ring in the 3-substituent. The other two variables are also seen to produce positive effects on the activity of the compounds, but while I_1, signifying the effect of cycloalkyl ring size, is statistically significant at 95% confidence level (data within parenthesis), I_2, delineating the effect of unsaturation of 5,6-bond, is not. However, since the coefficient of I_2 is positive, the unsaturation of the 5,6-bond would be preferred to its saturation.

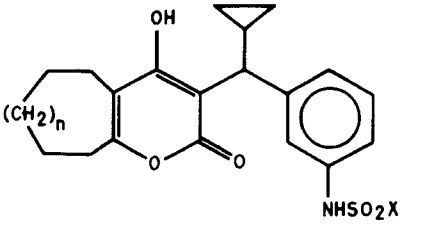
$$\log(1/K_i) = 0.546(\pm 0.504)I_1 + 0.429(\pm 0.454)I_2 + 4.032(\pm 0.454)I_3 + 5.809$$
$$n = 15, \quad r = 0.986, \quad s = 0.39, \quad F_{3,11} = 127.20 \qquad (1)$$

The other values of n were also taken for I_1, but the best correlation was obtained with $n=4$ only. n was also used as variable with all its values 1–6, but it was found to be statistically insignificant. Thus a cyclooctyl ring was found to be optimal. This fact was also verified in Table II, where primarily the variation in the 3′-sulfonamide group was studied.[13] A highly significant correlation (Eq. (2)) was obtained between the binding constant of the compounds and the calculated hydrophobic constant (π) of the X moiety at the sulfonamide group and an indicator variable $I=1$ for $n=2$ in the cycloalkyl ring. The correlation shows that $n=2$ (a cyclooctyl ring) will give 10-fold higher activity than $n=1$ (a cycloheptyl ring), for which $I=0$. The correlation of activity with π_x suggests that the X moiety of the sulfonamide may have the hydrophobic interaction with the receptor, but since the correlation is parabolic and π_x attains an optimum value equal to 2.79, the receptor site may be assumed to have limited bulk tolerance, since in *in vitro* system there is no membrane-like lipid–water transport barrier to optimize the role of hydrophobicity.

$$\log(1/K_i) = 0.762(\pm 0.407)\pi_x - 0.136(\pm 0.085)\pi_x^2 + 0.870(\pm 0.293)I + 6.551$$
$$n = 10, \quad r = 0.979, \quad s = 0.13, \quad F_{3,6} = 47.21 \qquad (2)$$

In deriving Eq. (2), however, compound **8** (Table II) has not been included, as it behaved as an outlier. Its observed activity is much lower than that

TABLE II Cycloalkylpyranones studied by Skulnick *et al.*[13] and their HIV-1-PR binding affinity



Compound no.	*n*	*X*	π_X	*I*	log(1/K_i)	
					Observed	*Calculated Eq.* (2)
1	1	CH_3	0.56	0	6.92	6.93
2	1	CH_2CH_3	1.02	0	7.20	7.19
3	1	$CH{=}CH_2$	0.82	0	—	7.08
4	2	CH_3	0.56	1	7.96	7.80
5	2	CH_2CH_3	1.02	1	8.00	8.06
6	2	$CH{=}CH_2$	0.82	1	7.75	7.95
7	2	*n*-Pr	1.55	1	8.40	8.27
8	2	*i*-Pr	1.53	1	7.48	8.27
9	2	*n*-Bu	2.13	1	8.34	8.42
10	2	*n*-Octyl	4.20	1	8.22	8.21
11	2	C_6H_5	1.96	1	8.50	8.39
12	2	Cyclohexyl	2.76	1	8.44	8.48

predicted by Eq. (2) (Table II). This low activity of the compound can be attributed to the branched character of the *X* moiety which may produce some steric effects.

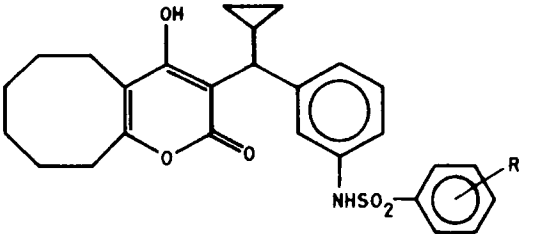
Also in deriving Eq. (1) compounds **5**, **11**, and **13** (Table I) were not included because of their uncertain activity data. The equation, however, predicts their activity as 6.24, 5.81, and 5.81, respectively.

Table III contains a series of cyclooctylpyranones, where a study has been made[13] on the effect of substitution at the aryl portion of the 3′-arylsulfonamide group. For this series, the best equation that we could obtain was

$$\log(1/K_i) = 9.948 - 0.564(\pm 0.194)B5_2 - 0.118(\pm 0.073)B5_4 - 0.774(\pm 0.239)B5_5 + 0.662(\pm 0.328)D_{CN}$$
$$n = 43, \quad r = 0.856, \quad s = 0.21, \quad F_{4,38} = 26.07 \qquad (3)$$

where B5 is Verloop's STERIMOL parameter defining the maximum width of the substituents,[19] and D_{CN} is an indicator variable used with a value of unity for a CN group present at the 3- or 4-position. If this

TABLE III Cyclooctylpyranones studied by Skulnick *et al.*[13] and their HIV-1-PR binding affinity



Compound no.	*R*	$B5_2$	$B5_4$	$B5_5$	D_{CN}	$\log(1/K_i)$	
						Observed	*Calculated Eq.* (3)
1	H	1.00	1.00	1.00	0	8.50	8.53
2	2-Me	2.04	1.00	1.00	0	8.03	7.95
3	2-F	1.35	1.00	1.00	0	7.96	8.34
4	2-Cl	1.80	1.00	1.00	0	8.03	8.08
5	2-CF_3	2.61	1.00	1.00	0	7.68	7.62
6	2-CN	1.60	1.00	1.00	0	8.13	8.19
7	3-Me	1.00	1.00	1.00	0	8.28	8.53
8	3-Cl	1.00	1.00	1.00	0	8.57	8.53
9	3-Br	1.00	1.00	1.00	0	8.59	8.53
10	3-CF_3	1.00	1.00	1.00	0	8.52	8.53
11	3-NO_2	1.00	1.00	1.00	0	8.33	8.53
12	3-COOH	1.00	1.00	1.00	0	8.35	8.53
13	3-CO_2Me	1.00	1.00	1.00	0	8.85	8.53
14	3-NH_2	1.00	1.00	1.00	0	8.64	8.53
15	3-CN	1.00	1.00	1.00	1	9.22	9.19
16	4-Me	1.00	2.04	1.00	0	8.48	8.41
17	4-Et	1.00	3.17	1.00	0	8.30	8.28
18	4-*n*-Pr	1.00	3.49	1.00	0	7.96	8.24
19	4-*i*-Pr	1.00	3.17	1.00	0	7.89	8.28
20	4-*t*-Bu	1.00	3.17	1.00	0	7.50	8.28
21	4-F	1.00	1.35	1.00	0	8.51	8.49
22	4-Cl	1.00	1.80	1.00	0	8.60	8.44
23	4-Br	1.00	1.95	1.00	0	8.68	8.42
24	4-I	1.00	2.15	1.00	0	8.51	8.40
25	4-CF_3	1.00	2.61	1.00	0	8.21	8.34
26	4-CN	1.00	1.60	1.00	1	9.10	9.13
27	4-NO_2	1.00	2.44	1.00	0	8.57	8.36
28	4-CO_2H	1.00	2.66	1.00	0	7.96	8.34
29	4-$CONH_2$	1.00	3.07	1.00	0	8.72	8.29
30	4-OMe	1.00	3.07	1.00	0	8.41	8.29
31	4-O-*n*-Bu	1.00	4.79	1.00	0	7.75	8.09
32	4-OCF_3	1.00	3.61	1.00	0	8.40	8.23
33	4-NH_2	1.00	1.97	1.00	0	8.16	8.42
34	4-NMe_2	1.00	1.35	1.00	0	8.55	8.49
35	4-N_3	1.00	4.18	1.00	0	8.59	8.16
36	2,6-diMe	2.04	1.00	1.00	0	< 6.70	7.95
37	2,6-diCl	1.80	1.00	1.00	0	< 6.70	8.08
38	2,5-diCl	1.80	1.00	1.80	0	7.13	7.46
39	2,4-diCl	1.80	1.80	1.00	0	8.21	7.99

TABLE III (*Continued*)

Compound no.	*R*	$B5_2$	$B5_4$	$B5_5$	D_{CN}	$\log(1/K_i)$	
						Observed	*Calculated Eq.* (3)
40	2,4-diF	1.35	1.35	1.00	0	8.39	8.29
41	2,3-diCl	1.80	1.00	1.00	0	8.12	8.08
42	3,5-diCl	1.00	1.00	1.80	0	8.16	7.91
43	3,5-diCF_3	1.00	1.00	2.61	0	7.33	7.29
44	3,4-diCl	1.00	1.80	1.00	0	8.39	8.44
45	3,4-diOCH_3	1.00	3.07	1.00	0	8.17	8.29
46	2,3,4-triCl	1.80	1.80	1.00	0	8.06	7.99

indicator variable is used for 2-CN also, a slightly poorer correlation is obtained (Eq. (4)), exhibiting a reduced effect of the 2-CN ring substitution. A positive coefficient of this variable in both Eqs. (3) and (4), thus, indicates that a CN substitution at the ring would be beneficial with a dominant effect at the 3- or 4-position.

$$\log(1/K_i) = 10.059 - 0.612(\pm 0.209)B5_2 - 0.122(\pm 0.080)B5_4 - 0.778(\pm 0.261)B5_5 + 0.416(\pm 0.295)D_{CN}$$
$$n = 43, \quad r = 0.827, \quad s = 0.22, \quad F_{4,38} = 20.51 \qquad (4)$$

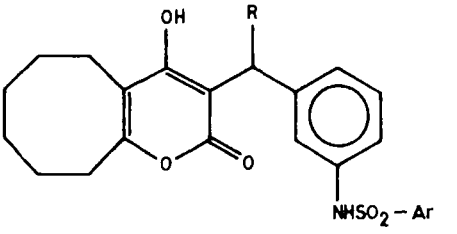
In both the equations, the negative coefficients of width parameter used for 2-, 4-, and 5-substituents suggest that all these substituents would produce steric effects. No physicochemical parameters for the 3-substituents were found to be significant, hence the 3-substituents were assumed to play no role in the binding of the compounds with the receptor.

The high coefficients of $B5_2$ and $B5_5$ as compared to that of $B5_4$ suggest that the 2- and 5-substituents have more detrimental effect than the 4-substituents. The beneficial effect of CN present at any position can be attributed to its highly polar nature and completely linear shape, so that it can be easily accommodated even in a narrowest site and have a strong dipole–dipole or any other kind of electronic interaction.

In the derivation of Eqs. (3) and (4), however, compounds **36** and **37** (Table III), due to having uncertain activity data, were not included. Another compound **20** was not included because it exhibited an aberrant behaviour. Its observed activity (7.50) is shown to be much less than predicted by Eq. (3) (8.28). This difference can be attributed to the bulk of 4-t-Bu substituent, whose effect probably cannot be accounted for by only a width parameter but by its total molar volume.

The fairly low activity of compounds **36** and **37** can be due to the presence of substituents at both the ortho positions, which together might be producing very strong steric effects.

TABLE IV Cyclooctylpyranones studied by Skulnick *et al.*[13] and their HIV-1-PR binding affinity



Compound no.	*Ar*	*R*	I_1	I_2	I_3	I_4	log(1/K_i)		
							Observed	*Calculated Eq.* (5)	*Calculated Eq.* (6)
1	*p*-Cl-Ph	*c*-Pr	0	0	0	1	8.60	8.63	8.52
2	*p*-Cl-Ph	Et	0	0	0	0	8.46	8.47	8.52
3	*p*-Cl-Ph	*n*-Pr	0	0	0	0	8.40	8.47	8.52
4	*p*-Cl-Ph	*i*-Pr	0	0	1	0	7.75	7.93	7.93
5	*p*-CN-Ph	*c*-Pr	0	1	0	1	9.10	8.93	8.80
6	*p*-CN-Ph	Et	0	1	0	0	8.51	8.76	8.80
7	*p*-CN-Ph	*n*-Pr	0	1	0	0	8.85	8.76	8.80
8	*p*-CN-Ph	*n*-Bu	0	1	0	0	8.68	8.76	8.80
9	*p*-CN-Ph	*i*-Pr	0	1	1	0	8.23	8.22	8.21
10	*p*-CN-Ph	CH_2-*i*-Pr	0	1	0	0	8.82	8.76	8.80
11	*p*-F-Ph	*c*-Pr	0	0	0	1	8.51	8.63	8.52
12	*p*-F-Ph	*n*-Pr	0	0	0	0	8.68	8.47	8.52
13	*p*-F-Ph	*n*-Bu	0	0	0	0	8.22	8.47	8.52
14	*p*-F-Ph	*i*-Pr	0	0	1	0	7.96	7.93	7.93
15	*p*-F-Ph	CH_2-*i*-Pr	0	0	0	0	8.55	8.47	8.52
16	N-Me-imidazole	*c*-Pr	1	0	0	1	9.95	10.08	9.98
17	N-Me-imidazole	*n*-Pr	1	0	0	0	10.00	9.92	9.98
18	N-Me-imidazole	*i*-Pr	1	0	1	0	9.30	9.38	9.39
19	N-Me-imidazole	CH_2-*i*-Pr	1	0	0	0	10.07	9.92	9.98
20	8-Quinoline	*c*-Pr	0	0	0	1	8.72	8.63	8.52
21	8-Quinoline	*n*-Pr	0	0	0	0	8.68	8.47	8.52
22	8-Quinoline	*i*-Pr	0	0	1	0	8.38	7.93	7.93
23	8-Quinoline	CH_2-*i*-Pr	0	0	0	0	8.48	8.47	8.52
24	3-Pyridyl	*c*-Pr	0	0	0	1	8.66	8.63	8.52
25	3-Pyridyl	*n*-Pr	0	0	0	0	8.66	8.47	8.52
26	3-Pyridyl	*i*-Pr	0	0	1	0	7.70	7.93	7.93
27	3-Pyridyl	CH_2-*i*-Pr	0	0	0	0	8.03	8.47	8.52

In another series (Table IV) too, the variation in the aryl moiety of the sulfonamide group was studied along with the variation at C-3α of the 3-alkyl substituent.[13] A Fujita–Ban analysis was performed to find out the activity contribution of each different aryl moiety and of each different alkyl group at C-3α. Among the aryl groups, *p*-Cl-Ph and 3-pyridyl were found to make, though statistically insignificant, negative contributions and of the

remaining four, which were found to make positive contributions, the most dominant effect was found to be associated with the N-Me-imidazole group and the next with the *p*-CN-Ph group. The contributions of the other two, i.e., *p*-F-Ph and 8-quinoline, though positive, were found to be statistically insignificant.

Among the alkyl groups at C-3α, a statistically significant but negative contribution was found to be associated with the isopropyl group and a positive contribution, though only marginally significant statistically but more than those of others, with *c*-propyl. Thus, the two aryl groups, N-Me-imidazole and *p*-CN-Ph, and the two C-3α substitutes, *i*-pr and *c*-propyl, were found to dominate the binding affinity, accounting for 91% of the variance in it (Eq. (5), $r^2 = 0.91$). Their effects have been described by indicator variables I_1, I_2, I_3, and I_4, respectively, with a value of 1 each. If the variable I_4, used for cyclopropyl, is dropped, as in comparison to others it is statistically less significant, the correlation remains almost unaffected (Eq. (6)), still accounting for 89% of the variance in the binding affinity ($r^2 = 0.89$).

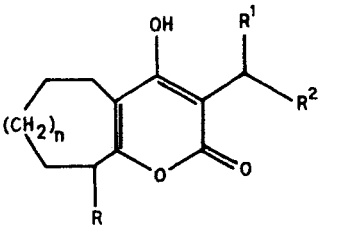
$$\log(1/K_i) = 1.457(\pm 0.229)I_1 + 0.295(\pm 0.197)I_2 - 0.539(\pm 0.200)I_3 + 0.165(\pm 0.200)I_4 + 8.466$$
$$n = 27, \quad r = 0.953, \quad s = 0.20, \quad F_{4,22} = 54.20 \qquad (5)$$

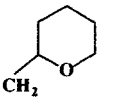
$$\log(1/K_i) = 1.461(\pm 0.238)I_1 + 0.281(\pm 0.204)I_2 - 0.588(\pm 0.199)I_3 + 8.516$$
$$n = 27, \quad r = 0.946, \quad s = 0.21, \quad F_{3,23} = 65.74 \qquad (6)$$

However, both Eqs. (6) and (7) show that the activity contributions of the N-Me-imidazole group would be about 15 times greater than that of the *p*-CN-Ph group. This difference can be attributed to the presence in the former of a heterocyclic nitrogen ortho to the sulfonamide that can participate in the hydrogen bonding interaction with the NH of Asp29. This has been pointed out by Skulnick *et al.*[13] based on X-ray crystal structures of related sulfonamides bonded to HIV protease.[20] This theory also explains the predominant effect of 4-cyano-2-pyridinesulfonamide group, pointed out by the variable I_3 in Eq. (1) obtained for the compounds of Table I.

Although Eq. (5) does not show any significant role of *c*-propyl at C-3α among the various other substituents tried at this position, this group was found to be the best. In Table V its effect has been reported against Et. It was also tried as a replacement of the phenyl group, the second substituent

TABLE V Cycloalkylpyranones studied by Romines *et al.*[11] and their HIV-1-PR binding affinity



Compound no.	*n*	R^1	R^2	*R*	I_1	I_2	I_R	I_n	log(1/K_i)	
									Observed	*Calculated Eq.* (7)
1	2	Et	Ph	H	0	0	0	1	7.23	7.19
2	2	Et	Ph	Me	0	0	1	1	6.48	6.47
3	2	Et	Ph	CH_2-Ph	0	0	1	1	6.56	6.63
4	2	*c*-Pr	*c*-Pr	H	1	1	0	1	7.24	7.19
5	2	*c*-Pr	*c*-Pr	CH_2-Ph	1	1	1	1	6.59	6.64
6	2	*c*-Pr	Ph	H	1	0	0	1	7.93	7.65
7	2	*c*-Pr	Ph	Et	1	0	1	1	7.48	7.50
8	2	*c*-Pr	Ph	*n*-Pr	1	0	1	1	7.59	7.70
9	2	*c*-Pr	Ph	*n*-Bu	1	0	1	1	7.51	7.59
10	2	*c*-Pr	Ph	CH_2-*i*-Pr	1	0	1	1	7.52	7.66
11	2	*c*-Pr	Ph	CH_2-*c*-Pr	1	0	1	1	7.62	7.58
12	2	*c*-Pr	Ph	$(CH_2)_2$-*i*-Pr	1	0	1	1	7.30	7.32
13	2	*c*-Pr	Ph		1	0	1	1	6.92	6.87
14	1	*c*-Pr	Ph	H	1	0	0	0	7.02	7.40
15	1	*c*-Pr	Ph	$(CH_2)_2OCH_3$	1	0	1	0	7.55	7.46
16	1	*c*-Pr	Ph	CH_2-*c*-Pr	1	0	1	0	7.62	7.33

at C-3α (R^2). A relative assessment of it, both as R^1 and R^2, was made using an indicator variable I_1 equal to 1 for $R^1 = c$-propyl and zero for $R^1 = $ Et, and another variable I_2 equal to 1 for $R^2 = c$-propyl and zero for $R^2 = $ Ph, and then obtaining the equation,

$$\log(1/K_i) = 0.879(\pm 0.294)I_1 - 0.827(\pm 0.356)I_2 - 0.594(\pm 0.301)I_R + 7.160$$
$$n = 15, \quad r = 0.919, \quad s = 0.197, \quad F_{3,11} = 19.79 \qquad (7)$$

which showed that $R^1 = c$-propyl would be preferred to $R^1 = $ Et and that $R^2 = c$-propyl would be less advantageous than $R^2 = $ Ph. The additional

parameter I_R in Eq. (7) is to account for the effect of the R substituent of the cycloalkyl ring. For any R substituent it is equal to 1 and zero for no substituent. From its negative coefficient it is obvious that no R substituent at the cycloalkyl ring would be advantageous.

In deriving Eq. (7), however, compound **14** (Table V) has not been included. It behaves as an outlier. This compound is similar to compound **6**, except that it is an heptyl ring instead of an octyl ring. Its low activity as compared to that of compound **6** should be attributed to this difference, but when a parameter I_n is used to account for this difference with a value of 1 for octyl ring and zero for heptyl ring, no statistical significance of it is obtained nor is there obtained any significant improvement in the correlation (Eq. (8)).

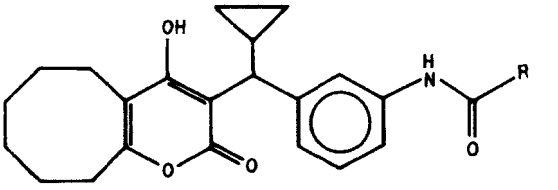
$$\log(1/K_i) = 0.847(\pm 0.299)I_1 - 0.789(\pm 0.380)I_2 - 0.611(\pm 0.302)I_R - 0.179(\pm 0.343)I_n + 7.249$$
$$n = 16, \quad r = 0.929, \quad s = 0.194, \quad F_{4,11} = 15.64 \tag{8}$$

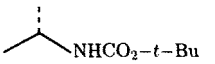
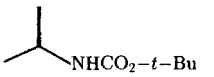
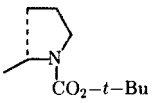
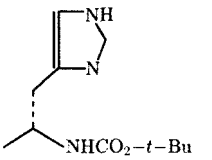
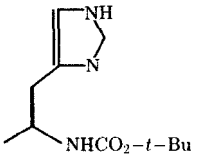
In addition to sulfonamide derivatives, a series of carboxamide derivatives (Table VI) was also studied,[11] in which the R-moiety of carboxamide group was varied. We found a good correlation between the calculated π values of various R-moieties and the activity of the compounds as shown by,

$$\log(1/K_i) = 8.480 - 0.750(\pm 0.397)\pi_R$$
$$n = 17, \quad r = 0.721, \quad s = 0.50, \quad F_{1,15} = 16.20 \tag{9}$$

This correlation suggests that a lipophilic R-moiety will not be beneficial to the activity. The correlation, however, accounts for only 52% of the variance in the activity. A significant improvement in it was achieved (Eq. (10)) when an indicator variable I equal to 1 was used for compounds **12-15** (Table VI). In these compounds, the R-moieties provide a hydrogen-bond donor or acceptor group just adjacent to the amide group (NH-CO), and the negative coefficient of I indicates that such moieties would not be favourable to the binding. It can be assumed that these moieties can form intramolecular hydrogen bonds with NH or CO of the amide group and thus hinder their interaction with the receptor. The correlation now, however, accounts for 75% variance in the binding affinity and is further improved significantly to account for 88% of the variance when compounds

TABLE VI Cyclooctylpyranones studied by Romines *et al.*[11] and their HIV-1-PR binding affinity



Compound no.	*R*	π	*I*	$\log(1/K_i)$	
				Observed	*Calculated Eq.* (11)
1	Ph	1.49	0	7.38	7.51
2	*p*-F-Ph	1.83	0	7.26	7.27
3	$CH_2CH=CHPh$	2.65	0	6.33	6.72
4	$CH_2CH_2NHCO_2$-*t*-Bu	0.91	0	8.26	7.99
5	$CH_2CH_2CH_2NHCO_2$-*t*-Bu	1.24	0	8.40	7.68
6	$CH_2CH_2CH_2CH_2NHCO_2$-*t*-Bu	0.91	0	7.85	7.90
7		1.13	0	8.16	7.75
8		1.22	0	7.49	7.69
9		2.09	0	7.37	7.10
10		0.23	0	8.52	8.36
11		0.23	0	7.96	8.36
12	NHEt	0.47	1	7.14	7.24
13	NHPh	1.86	1	6.35	6.30
14	OEt	1.13	1	7.72	6.79
15	OPh	2.11	1	6.18	6.13
16	CH_2Et	1.05	0	7.62	7.80
17	CH_2Ph	1.76	0	7.48	7.32

5 and **14** are excluded from the regression (Eq. (11)). For both the compounds, Eq. (11) predicts a fairly low activity as compared to their corresponding observed activity (Table VI). The reason of this difference seems hard to explain.

$$\log(1/K_i) = 8.622 - 0.718(\pm 0.297)\pi_R - 0.780(\pm 0.459)I$$
$$n = 17, \quad r = 0.868, \quad s = 0.374, \quad F_{2,14} = 21.36 \qquad (10)$$

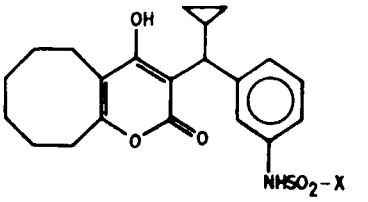
$$\log(1/K_i) = 8.518 - 0.680(\pm 0.215)\pi_R - 0.961(\pm 0.374)I$$
$$n = 15, \quad r = 0.938, \quad s = 0.27, \quad F_{2,12} = 43.89 \qquad (11)$$

The use of any steric parameter in place of π_R was not found to be successful. Hence the negative dependence of the activity on π_R cannot be attributed to any kind of steric effect of the R substituent but purely to its hydrophobic nature. Therefore, to have the positive effect one should take the hydrophilic (polar) substituents, which might have a polar interaction with the receptor.

On the basis of these studies, we derive the following conclusions.

1. In cycloalkyl rings, a cyclooctyl ring with unsaturation in the 5,6-bond appears to be optimal.
2. At the 3-position of the pyranone ring, a cyclopropyl- and phenyl-substituted methyl group would be preferred.
3. Substitution at the meta position of the phenyl ring of the 3-substituent is found to enhance the activity and a 4-cyano-2-pyridinesulfonamide group is found to be the best.
4. A hydrophobic substituent on the sulfonamide would increase the binding affinity, provided it is not very bulky. It is assumed to have a hydrophobic interaction with the receptor. From this point of view an aryl substituent is found to be better than an alkyl substituent.
5. In the arylsulfonamides, if the aryl group is substituted, only a cyano group at the 3- or 4-position is found to be advantageous. However, in place of a 3- or 4-cyanophenyl, an N-Me-imidazole group is found to be better.
6. If, in place of a sulfonamide group, a carboxamide group is used, the presence of a polar substituent can increase the activity. However, carboxamide derivatives were found to be less active than sulfonamide derivatives.

On the basis of the above findings, the following compounds seem to have a bright future.



3 X = 4-CN-2-pyridine
4 X = N-Me-imidazole
5 X = 3- or 4-CN-Ph

HIV proteases offer a number of possibilities for hydrogen bonding and in sulfonamides both NH and SO_2 moieties are assumed to form hydrogen bonds with the receptor.[10] We have already discussed how the above mentioned X substituents can further strengthen the binding of the molecule with the enzyme. In all X substituents the aromatic ring is assumed to have π-stacking interaction with the Arg 8 residue of the protease.[13]

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