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QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDIES ON SOME ANTI-HUMAN-IMMUNODEFICIENCY-VIRUS-1 (ANTI-HIV-1) DRUGS: VIRAL REVERSE TRANSCRIPTASE INHIBITORS

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The anti-HIV-1 activity of some 3-[(benzoxazol-2-ylmethyl)amino]-, 3-[(benzoxazol-2-yl)ethyl]-, 3-[*N*-(phthalimidomethyl)amino]- and 3-[*N*-(phthalimido)ethyl]-5-ethyl-6-methyl pyridin-2(1H)-one derivatives, that have been found to elicit their action through the allosteric inhibition of the enzyme viral reverse transcriptase (VRT), have been analysed in relation to the physicochemical properties of the molecules. Significant correlations were obtained between the activity and the hydrophobic and electronic constants of substituents and van der Waals' volume of the linker chain. Based on these findings the mechanism of action of these drugs is discussed.

Keywords: Quantitative structure-activity relationship; HIV-1 reverse transcriptase inhibitors; 2-pyridinone derivatives.

INTRODUCTION

The human immunodeficiency virus (HIV) is a pathogenic retrovirus and causative agent of acquired immunodeficiency syndrome (AIDS) and its related disorders. The development of potent and effective antiviral drugs for the control of human immunodeficiency virus type 1 (HIV-1) infection is one of the more pressing goals of contemporary medicinal chemistry. Since retroviruses, such as HIV-1, possess a unique replication cycle, a variety of molecular targets are available for chemotherapeutic intervention.[1] One such target is the enzyme viral reverse transcriptase (VRT) which mediates conversion of the viral RNA genome to proviral DNA. Nucleoside analogue, 3′-azido-2′,3′-dideoxy thymidine (AZT or Zidovudine)

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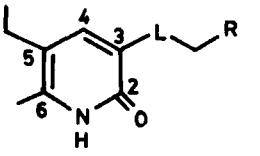
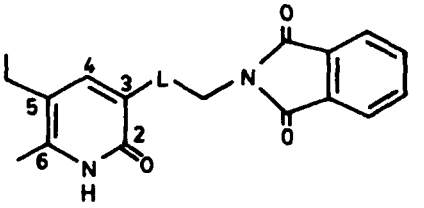
was discovered[2] to inhibit the infectivity and cytopathicity of HIV-1 at a very low concentration and, after many clinical studies and adequate trials, was approved for the treatment of HIV-1 infection. However, it was found to suffer from a number of limitations including some side effects and the revelation of the possible emergence of drug resistant mutants of the virus.[3,4]

Attention is, therefore, currently focussed on the development of other nucleoside and non-nucleoside inhibitors as alternative chemotherapeutic agents. Consequently, some authors[5] made a study on some 2-pyridinone derivatives (**I**),that are potent and selective non-nucleoside inhibitors of HIV-1 reverse transcriptase.

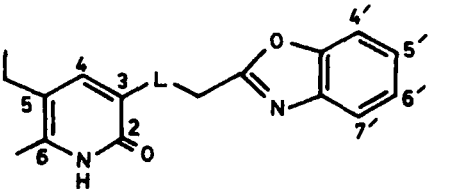


(I)

A detailed structure-activity relationship (SAR) related to 3-[*N*-(phthalimidomethyl)amino]-5-ethyl-6-methylpyridin-2(1H)-one(II), a lead compound discovered by screening, has been reported.[5] Although the pyridinone (**II**) was a potent VRT inhibitor, it was hydrolytically unstable under physiological conditions. Subsequent efforts focussed on improving the chemical stability of (**II**) yielded a few new derivatives (**III**)–(**V**).[6–8]



(II) L = NH
(III) L = CH_2



(IV) L = NH
(V) L = CH_2

These potent, specific, and hydrolytically stable VRT inhibitors had a high level of antiviral activity, but it was of short duration due to the rapid onset of viral resistance.[8] Further studies demonstrated the need for some specific substituents at specific positions on the pyridinone and aryl rings, and a flexible two-atom linker chain between these two rings. However, all these modifications were based only on trial-and-error methods. In order to reduce the trial-and-error factor, a

quantitative SAR (QSAR) on these drugs is proposed. The QSAR not only provides the rationales for the selection of subsituents but also throws light on the mechanism of action of the drugs. The present paper discusses the result of a QSAR study based on the data of Hoffman *et al.*[6–8]

MATERIALS AND METHODS

QSAR analysis was conducted on 2-pyridinone (**I**) derivatives studied by Hoffman *et al.*[6–8] Their anti HIV-1 data (Tables I–IV) were subjected to multiple regression analysis using some physicochemical and structural parameters. The values of the physicochemical parameters were taken from the literature,[9] and a structural parameter V_w was calculated as suggested by Moriguchi *et al.*[10] The V_w is a measure of molecular size that constitutes an important aspect of drug-receptor interaction. It characterizes the dispersion interaction or sometimes the steric effects in drug-receptor interaction and has been found to be very useful in QSAR studies.[11] Additionally, some indicator variables were also used to describe the effect of some specific modifications in the compounds.

The anti-HIV-1 data refer to the ability of compounds to inhibit the HIV-1 reverse transcriptase. They have been reported in terms of IC_{50}, the minimum concentration of the compound producing 50% inhibition of the enzyme. A multiple regression analysis using a least square method was adopted to derive all QSAR equations.[12]

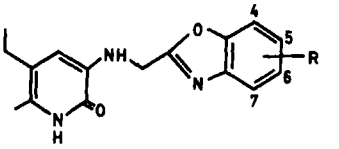
RESULTS AND DISCUSSION

Table I lists the compounds where significant alterations were made in the R-substituent of the aryl ring of 3-[(benzoxazol-2-ylmethyl)amino]-5-ethyl-6-methylpyridin-2(1H)-one (**IV**). When a multiple regression analysis was performed, using various physicochemical parameters for the R-substituent, a significant correlation was obtained as shown by,

$$\log(1/IC_{50}) = 1.432(\pm 0.437)\pi_{4,7} - 0.906(\pm 0.777)\sigma_R - 0.572(\pm 0.470)(\pi_{4,7})^2 - 1.320(\pm 1.419)\pi_{5,6} + 6.521$$
$$n = 20, s = 0.47, r = 0.887, F_{4,15} = 13.85 \quad (1)$$

where 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 are 95% confidence intervals.

TABLE I Pyridinone (**IV**) derivatives studied by Saari *et al.*[7], their anti-HIV-1 activity, and physicochemical parameters



Compound	*R*	$(\pi_{4,7})^a$	$(\pi_{5,6})^a$	$(\sigma_R)^a$	$\log(1/IC_{50})$		
					Obsd.[b]	*Calcd. Eqn. (1)*	*Calcd. Eqn. (2)*
1	H	0.00	0.00	0.00	6.68	6.53	6.55
2	4-Me	0.56	0.00	–0.17	6.92	7.31	7.44
3	5-Me	0.00	0.56	–0.07	5.90	5.86	5.87
4	6-Me	0.00	0.56	–0.07	5.78	5.86	5.87
5	7-Me	0.56	0.00	–0.17	7.26	7.31	7.44
6	7-Et	1.02	0.00	–0.15	6.59[c]	7.53	7.77
7	4,7-Me_2	1.12	0.00	–0.34	7.70	7.72	7.99
8	4-Cl	0.71	0.00	0.23	6.82	7.06	7.14
9	7-Cl	0.71	0.00	0.23	7.19	7.06	7.14
10	4,7-Cl_2	1.42	0.00	0.46	7.72	6.99	7.19
11	4-F	0.14	0.00	0.06	6.96	6.67	6.69
12	5-F	0.00	0.14	0.34	6.33	6.04	6.00
13	6-F	0.00	0.14	0.34	5.90	6.04	6.00
14	7-F	0.14	0.00	0.06	7.04	6.67	6.69
15	4-F,7-Cl	0.85	0.00	0.29	6.98	7.08	7.18
16	4,7-F_2	0.28	0.00	0.12	7.15	6.78	6.82
17	4-OMe	–0.02	0.00	–0.27	6.74	6.75	6.81
18	4-OH	–0.67	0.00	–0.37	6.36	5.65	5.66
19	4-NO_2	–0.28	0.00	0.78	4.61	5.37	5.24
20	4-NH_2	–1.23	0.00	–0.66	4.17	4.51	4.52

[a]Taken from ref. 9. [b]Taken from ref. 7. [c]Not used in the derivation of Equation (2).

The parameter $\pi_{x,y}$ refers to the hydrophobic constant of the R-substituent at x- or/and y-position(s) of the benzoxazole ring and the parameter σ_R refers to the electronic constant (Hammett constant) of the same at any position(s) of the ring. Of these parameters, the $\pi_{5,6}$ does not appear to be significant at 95% confidence interval. However, when compound **6**, the only compound with $R = Et$ in the Table, is deleted not only does this parameter become significant but a notable improvement is observed in the whole correlation Equation (2). The negative

coefficient of $\pi_{5,6}$ expresses that the hydrophobic property of the R-substituent present at 5- or 6-position will decrease the activity. This may be probably due to the hydrophilic nature of the receptor site facing towards the 5- and 6-substituents. Such a receptor site would always prefer a hydrophilic subtituent rather than a hydrophobic one.

$$\begin{aligned}\log(1/IC_{50}) &= 1.569(\pm 0.389)\pi_{4,7} - 1.077(\pm 0.678)\sigma_R \\ &\quad - 0.526(\pm 0.403)(\pi_{4,7})^2 - 1.335(\pm 1.210)\pi_{5,6} + 6.544 \\ &\quad n = 19, s = 0.40, r = 0.926, F_{4,14} = 20.97 \end{aligned} \tag{2}$$

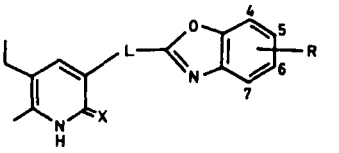
However, the activity is found to increase with the hydrophobic nature of 4- or/and 7-substituent(s), but since the correlation is parabolic in $\pi_{4,7}$, the activity is optimized with a value of $\pi_{4,7} = 1.49$. This limit to *in vitro* activity imposed by hydrophobicity can be attributed to the limited steric bulk tolerance at the active site of the receptor, as there are no transport barriers such as intervening membranes or non-selective binding to extraneous biological material in *in vitro* system. Within that limit, the 4,7-substituents can be involved in hydrophobic interaction with the receptor. Equation (2) is capable of accounting for 86% of variance ($r^2 = 0.86$) in the activity and its F-value is highly significant at the 99% level [$F_{4,14}(0.01) = 5.03$].

The effect of alterations in the linker chain L and substituent R of 3-[(benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1H)-one (**V**) (Table II) was also analysed[8] taking the hydrophobic and electronic constants of the R-substituent and the van der Waals' volume of the linker chain. The most significant correlation obtained was as shown by Equation (3),

$$\begin{aligned}\log(1/IC_{50}) &= 9.104(\pm 2.646)V_{w,L} - 1.156(\pm 0.338)(V_{w,L})^2 \\ &\quad + 0.261(\pm 0.370)\pi_R - 1.043(\pm 0.714)I_{5,6} \\ &\quad + 0.159(\pm 0.487)I_X - 10.578 \\ &\quad n = 33, s = 0.53, r = 0.862, F_{5,27} = 15.59 \end{aligned} \tag{3}$$

in which an indicator variable I_x was also used to account for the presence of sulphur (compounds **1–8**, Table II) instead of oxygen at the 2-position of the pyridinone ring with a value of unity for the former and zero for the latter. The parameters π_R and I_x didn't appear to be significant in the equation, but when compound **25** (Table II), which was showing aberrant behaviour was deleted, the parameter π_R became significant and correlation was also highly improved (Equation (4)).

TABLE II Pyridinone (V) derivatives studied by Hoffman *et al.*[d], their anti-HIV-1 activity, and physicochemical parameters



Compound	*R*	*-L-*	*X*	$(\pi_R)^a$	$(V_{w,L})^b$	log(1/IC$_{50}$)		
					(10^2 Å^3)	*Obsd.*[c]	*Calcd. Eqn. (5)*	*Calcd. Eqn. (6)*
1	H	$-CH_2CH_2-$	S	0.00	3.86	7.62	7.40	7.16
2	4,7-Me_2	$-CH_2CH_2-$	S	1.12	3.86	7.28	7.60	7.70
3	4,7-Cl_2	$-CH_2CH_2-$	S	1.42	3.86	7.52	7.67	7.70
4	4,7-F_2	$-CH_2CH_2-$	S	0.28	3.86	7.82	7.44	7.70
5	4-F	$-CH_2CH_2-$	S	0.14	3.86	7.89	7.61	7.70
6	7-F	$-CH_2CH_2-$	S	0.14	3.86	7.37	7.67	7.70
7	4-Cl	$-CH_2CH_2-$	S	0.71	3.86	7.52	7.44	7.70
8	7-Cl	$-CH_2CH_2-$	S	0.71	3.86	7.54	7.77	7.63
9	H	$-CH_2CH_2-$	O	0.00	3.86	7.64	7.89	7.63
10	4-Me	$-CH_2CH_2-$	O	0.56	3.86	7.48	7.42	7.63
11	4-Cl	$-CH_2CH_2-$	O	0.71	3.86	7.21	6.41	6.29
12	4-F	$-CH_2CH_2-$	O	0.14	3.86	7.82	6.24	6.29
13	7-Me	$-CH_2CH_2-$	O	0.56	3.86	7.40	6.24	6.29
14	7-Cl	$-CH_2CH_2-$	O	0.71	3.86	7.41	7.34	7.10
15	7-F	$-CH_2CH_2-$	O	0.14	3.86	7.43	7.80	7.64
16	4,7-Me_2	$-CH_2CH_2-$	O	1.12	3.86	7.55	7.92	7.64
17	4,7-Cl_2	$-CH_2CH_2-$	O	1.42	3.86	7.85	7.45	7.64
18	4,7-F_2	$-CH_2CH_2-$	O	0.28	3.86	7.85	7.40	7.64
19	6-Me	$-CH_2CH_2-$	O	0.56	3.86	6.76	7.40	7.64
20	6-F	$-CH_2CH_2-$	O	0.14	3.86	6.35	7.63	7.64
21	5-F	$-CH_2CH_2-$	O	0.14	3.86	5.77	7.63	7.64
22	H	$-OCH_2-$	O	0.00	3.17	6.72	6.63	7.04
23	4,7-Cl_2	$-OCH_2-$	O	1.42	3.17	7.06	7.21	7.04
24	4,7-Cl_2	$-SCH_2-$	O	1.42	3.40	7.96	7.59	7.40
25	4,7-Cl_2	$-S(O)CH_2-$	O	1.42	4.24	5.85[d]	7.90	7.63
26	4,7-Cl_2	$-SO_2CH_2$	O	1.42	5.08	6.69	6.49	6.38
27	H	$-NHCH_2-$	O	0.00	3.00	6.68	6.27	6.18
28	4,7-Cl_2	$-NHCH_2-$	O	1.42	3.00	7.70	6.85	6.72
29	H	$-CH_2NH-$	O	0.00	3.00	5.90	6.27	6.18
30	H	-CH=CH-(trans)	O	0.00	2.88	5.23	5.98	5.92
31	H	-CH=CH-(cis)	O	0.00	2.88	5.52	5.98	5.92
32	H	$-CH_2-$	O	0.00	2.32	4.35	4.14	4.30
33	H	$-(CH_2)_3-$	O	0.00	5.40	4.80	4.94	4.98

[a]Taken from ref. 9. [b]Calculated according to ref. 11. [c]Taken from ref. 8. [d]Not used In the derivation of Equations (5) and (6).

$$\log(1/IC_{50}) = 9.497(\pm 1.985)V_{w,L} - 1.197(\pm 0.253)(V_{w,L})^2 + 0.409(\pm 0.284)\pi_R - 1.129(\pm 0.535)I_{5,6} - 0.031(\pm 0.368)I_X - 11.421$$
$$n = 32, s = 0.40, r = 0.925, F_{5,26} = 30.93 \quad (4)$$

However the parameter I_x still remained insignificant and following its deletion a new equation was obtained without any loss in the significance of correlation (Equation (5)). Thus it was found that the replacement of oxygen by sulphur at the 2-position of pyridinone ring is of little advantage. Equation (5) expresses a highly significant correlation and accounts for 86% of the variance in the activity ($r^2 = 0.86$). Its F-value is highly significant at the 99% level [$F_{4,27}(0.01) = 4.11$]. From this equation, the size of the linker chain is found to have a significant effect on the activity. This may be probably due to the involvement of the linker chain in some dispersion interaction with the receptor, as the van der Waals' volume is indicative of this kind of interaction. However, since there is a parabolic correlation between the activity and $V_{w,L}$, the activity is optimized with a $V_{w,L}$ value of 3.97×10^2 Å^3. Beyond this value, $V_{w,L}$ will lead to a decrease in the activity, suggesting that the receptor site with which the linker chain interacts possesses a limited bulk tolerance.

$$\log(1/IC_{50}) = 9.559(\pm 1.811)V_{w,L} - 1.204(\pm 0.233)(V_{w,L})^2 + 0.408(\pm 0.277)\pi_R - 1.141(\pm 0.504)I_{5,6} - 11.565$$
$$n = 32, s = 0.39, r = 0.925, F_{4,27} = 40.09 \quad (5)$$

There is, however, a positive linear correlation between the activity and π_R, suggesting that a hydrophobic R-substituent will favour the activity. This substituent may be, therefore, expected to be involved in some hydrophobic interaction with the receptor. But since the indicator variable $I_{5,6}$, used with a value of unity to account for the specific effect of the R-substituent at the 5- or 6-position of the benzoxazole ring, has a negative coefficient, the R-substituent at these positions is indicated to have a detrimental effect. At these positions, therefore, this substituent seems to produce some steric effects. Thus the R-substituents at only the 4- and 7-positions seem to be important and it is found that if, instead of using $\pi_{4,7}$, simply an indicator variable $I_{4,7}$ is used with a value of unity to describe the effect of 4,7-substituents, an equally good correlation is obtained (Equation (6)). This suggests that these

$$\log(1/IC_{50}) = 8.430(\pm 2.320)V_{w,L} - 1.063(\pm 0.293)(V_{w,L})^2 + 0.540(\pm 0.446)I_{4,7} - 0.801(\pm 0.653)I_{5,6} - 9.539$$
$$n = 32, s = 0.41, r = 0.918, F_{4,27} = 36.26 \quad (6)$$

substituents will increase the activity irrespective of their physicochemical properties. A larger variety of these subsitutents needs to be studied to ascertain that it is only the hydrophobic property of the substituents that affects the activity.

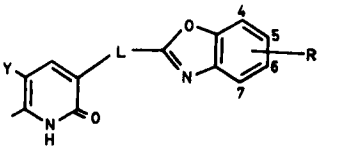
$$\log(1/IC_{50}) = 0.614(\pm 0.379)\pi_Y + 0.868(\pm 0.609)I_R - 0.138(\pm 0.295)(\pi_Y)^2 + 0.215(\pm 1.921)\sigma_Y - 0.040(\pm 0.650)I_L + 6.150$$
$$n = 24, s = 0.60, r = 0.832, F_{5,1} = 8.10 \quad (7)$$

The effect of alteration at the Y-position of the pyridinone ring (**IV** and **V**, Table III)[7,8] was also analysed, using the physicochemical properties of the Y-substituents, which resulted in Equation (7). In this equation, parameter I_R was used in place of $\pi_{4,7}$, as there were no variations in the R-substituent — it was either 4,7-Cl_2 or H, which could be described by I_R with a value of unity for the former and zero for the latter. Another indicator variable I_L was used to find which of the two groups $NHCH_2$ and CH_2CH_2 was more suitable as linker chain. It was assigned a value of unity for the former and zero for the latter. Equation (7) shows that a hydrophobic Y-substituent would favour the activity. I_R, being quite significant, indicates that the 4,7-dichloro aryl ring would be more favourable to the activity, whereas the parameter I_L, being insignificant, shows that the $NHCH_2$ linker group has no added advantage over the CH_2CH_2 group. After deletion of this parameter and also the insignificant electronic parameter σ_Y and the square term of π_Y, Equation (8) was obtained without any significant loss in the merit of the correlation.

$$\log(1/IC_{50}) = 0.553(\pm 0.246)\pi_Y + 0.937(\pm 0.524)I_R + 6.038$$
$$n = 24, s = 0.57, r = 0.822, F_{2,21} = 21.87 \quad (8)$$

Alterations at the L-,Y- and Z-positions for the derivatives of 3-[*N*-(phthalimidomethyl)amino]-5-ethyl-6-methylpyridin-2(1H)-one (**II**) and 3-[*N*-(phthalimido) ethyl]-5-ethyl-6-methylpyridin-2(1H)-one (**III**) were also examined[6] (Table IV), and for them the QSAR analysis revealed the equation,

TABLE III Pyridinone (IV) and (V) derivatives studied by Saari *et al.*[7,8], their anti-HIV-1 activity, and physicochemical parameter



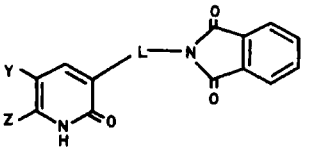
Compound	*R*	*-L-*	*Y*	$(\pi_y)^a$	$\log(1/IC_{50})$	
					Obsd.[b]	*Calcd. Eqn. (8)*
1	H	$-CH_2CH_2-$	Me	0.56	6.77	6.35
2	H	$-CH_2CH_2-$	Et	1.02	7.64	6.60
3	H	$-CH_2CH_2-$	n-Pr	1.55	7.08	6.90
4	H	$-CH_2CH_2-$	i-Pr	1.53	7.32	6.88
5	H	$-CH_2CH_2-$	Ph	1.96	5.96	7.12
6	H	$-CH_2CH_2-$	N≡C	–0.57	6.51	5.72
7	H	$-CH_2CH_2-$	$NHCOCH_3$	–0.97	4.38	5.50
8	H	$-CH_2CH_2-$	CH_2OH	–1.03	5.47	5.46
9	H	$-CH_2CH_2-$	CH_2OCH_3	–0.78	5.68	5.61
10	H	$-CH_2CH_2-$	NMe_2	0.18	5.73	6.14
11	4,7-Cl_2	$-CH_2CH_2-$	Me	0.56	7.01	7.29
12	4,7-Cl_2	$-CH_2CH_2-$	Et	1.02	7.85	7.54
13	4,7-Cl_2	$-CH_2CH_2-$	n-Pr	1.55	7.47	7.83
14	4,7-Cl_2	$-NHCH_2-$	SMe	0.61	7.37	7.31
15	4,7-Cl_2	$-NHCH_2-$	Et	1.02	7.72	7.54
16	4,7-Cl_2	$-NHCH_2-$	$CH=CH_2$	0.82	7.64	7.43
17	4,7-Cl_2	$-NHCH_2-$	OMe	–0.02	6.94	6.94
18	4,7-Cl_2	$-NHCH_2-$	$OCOCH_3$	–0.64	6.52	6.62
19	H	$-NHCH_2-$	Et	1.02	6.68	6.60
20	H	$-NHCH_2-$	SMe	0.61	6.72	6.38
21	H	$-NHCH_2-$	SEt	1.07	6.37	6.63
22	H	$-NHCH_2-$	SO_2Me	–1.63	5.94	5.14
23	H	$-NHCH_2-$	CO_2Et	0.51	5.76	6.32
24	H	$-NHCH_2-$	S(O)Me	–1.58	4.50	5.16

[a]Taken from ref. 9. [b] Taken from ref. 7,8.

$$\log(1/IC_{50}) = 3.452(\pm 2.406)\pi_Y + 2.991(\pm 0.926)I_L - 1.243$$
$$(\pm 1.101)(\pi_Y)^2 - 1.249(\pm 1.956)\pi_Z + 2.809$$
$$n = 13, s = 0.52, r = 0.947, F_{4,8} = 17.47 \quad (9)$$

in which π_Z seems to be statistically insignificant. However, on exclusion of compound **11** (Table IV), for which Equation (9) predicts very low activity as

TABLE IV Pyridinone (II) and (III) derivatives studied by Hoffman *et al.*[6], their anti-HIV-1 activity, and physicochemical parameters



Compound	*Y*	*Z*	*-L-*	$(\pi_Y)^a$	$(\pi_Z)^a$	log(1/IC$_{50}$)		
						Obsd.[b]	*Calcd. Eqn. (9)*	*Calcd. Eqn. (10)*
1	H	H	-NHCH$_2$-	0.00	0.00	5.78	5.80	5.80
2	H	Me	-NHCH$_2$-	0.00	0.56	5.09	5.10	5.10
3	Me	Me	-NHCH$_2$-	0.56	0.56	6.66	6.65	6.65
4	Et	Me	-NHCH$_2$-	1.02	0.56	7.52	7.33	7.33
5	n-Pr	Me	-NHCH$_2$-	1.55	0.56	7.24	7.47	7.47
6	n-Bu	Me	-NHCH$_2$-	2.13	0.56	6.89	6.81	6.81
7	Me	Et	-NHCH$_2$-	0.56	1.02	6.05	6.07	6.07
8	Et	Me	-NH(CH$_2$)$_2$-	1.02	0.56	4.35	4.34	4.12
9	Et	Me	-NH(CH$_2$)$_3$-	1.02	0.56	3.72	4.34	4.12
10	Et	Me	-CH$_2$-	1.02	0.56	4.58	4.34	4.12
11	Et	Me	-(CH$_2$)$_2$	1.02	0.56	5.43[c]	4.34	4.12
12	Et	Me	-(CH$_2$)$_3$-	1.02	0.56	3.68	4.34	4.12
13	Et	Me	-CH=CH-(trans)	1.02	0.56	4.27	4.34	4.12

[a]Taken from ref. 9. [b]Taken from ref. 6. [c]Not used in the derivation of Equation (10).

compared to its observed one, the correlation was found to be significantly improved (Equation (10)), with a statistically improved situation for π_Z.

$$\log(1/IC_{50}) = 3.452(\pm 1.538)\pi_Y + 3.209(\pm 0.608)I_L - 1.243(\pm 0.704)(\pi_Y)^2 - 1.249(\pm 1.250)\pi_Z + 2.590$$
$$n = 12,\ s = 0.32,\ r = 0.982,\ F_{4,7} = 48.36 \qquad (10)$$

Equation (10) is capable of accounting for 96% of the variance ($r^2 = 0.96$) in the activity and its F-value is highly significant at 99% level [$F_{4,7}(0.01) = 7.85$]. This equation, however, exhibits a parabolic correlation with π_Y, indicating that a hydrophobic Y-substituent is favourable for phthalimido pyridinone derivatives, but that there is an optimum value for $\pi_Y = 1.39$. The negative value of π_Z suggests that a highly hydrophobic Z-substituent will not be preferred. The indicator variable I_L

TABLE V Mutual Correlations (r-Values) of the variables used.

For Equation (2)	$\pi_{4,7}$	σ_R	$\pi_{5,6}$
$\pi_{4,7}$	1.00	0.37	0.16
σ_R		1.00	0.04
$\pi_{5,6}$			1.00

For Equations (5) and (6)	$V_{w,L}$	π_R	$I_{4,7}$	$I_{5,6}$
$V_{w,L}$	1.00	0.19	0.22	0.09
π_R		1.00	0.60	0.15
$I_{4,7}$			1.00	0.45
$I_{5,6}$				1.00

For Equation (10)	π_Y	I_X	π_Z
π_Y	1.00	0.17	0.25
I_X		1.00	0.04
π_Z			1.00

in Equation (10) was used for the linker chain L. It is equal to 1 for L =$NHCH_2$ and zero for L being any other group. Its high positive coefficient indicates that the $NHCH_2$ linker chain in this series of compounds is most suited for activity. In this case, probably the nitrogen of the phthalimido ring greatly polarizes the $NHCH_2$ group due to being directly attached to the linker chain and having a lone pair of electrons. This leads to a greater dispersion interaction of the $NHCH_2$ group with the receptor. Since in the $NHCH_2$ group there is also a lone pair of electrons on the nitrogen and since this electron pair is nearest, as compared to the electron pair present at any other linker group in the series, to the electron pair of the phthalimido nitrogen, this group suffers the greatest polarization.

All the variables used in any correlation were mutually orthogonal (Table V).

Now we can draw the following conclusions for the pyridinone derivatives (**IV**) and (**V**) from these correlation studies.

(1) A hydrophobic and electron donating R-substituent particularly at the 4- or/and 7-position(s) of the benzoxazole ring would be most favourable to the activity. The substituents on this ring are indicated to have strong hydrophobic interaction with the receptor, the enzyme viral reverse transcriptase (VRT). However, a limit to the activity would be imposed with increasing hydrophobicity.

(2) The R-substituent at either of the 5- and 6-positions would be detrimental to the activity.

(3) A hydrophobic Y-substituent in the pyridinone ring would favour the activity. This substituent may be assumed to have a hydrophobic interaction with the receptor.
(4) A two-atom linker chain of optimum size would also favour the activity due to its dispersion interaction with the receptor.

For the derivatives of phthalimido pyridinone (**II**) and (**III**), a Y-substituent of optimum hydrophobicity seems to favor the activity. It may be assumed to have a hydrophobic interaction with the receptor. In these derivatives, the $NHCH_2$ linker chain was found to be highly beneficial.

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