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QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDIES ON ANTI-HIV-1 TIBO DERIVATIVES AS INHIBITORS OF VIRAL REVERSE TRANSCRIPTASE

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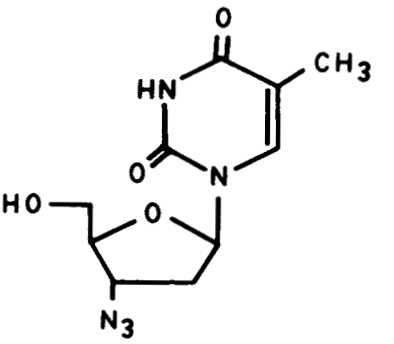
The anti-human-immunodeficiency-virus (HIV-1) activity of the derivatives of 4,5,6,7-tetrahydro-5-methylimidazo [4,5,1-jk] [1,4] benzodiazepin-2(1H)-one (TIBO) that have been found to elicit their action through the allosteric inhibition of the enzyme viral reverse transcriptase (VRT) is analysed in relation to the physicochemical properties of the molecules. Significant correlations are obtained between the activity and the hydrophobic constant and some dummy parameters of substituents. Based on these findings, the mechanism of action of these anti-HIV drugs is discussed.

Keywords: Quantitative structure-activity relationship, HIV-1 reverse transcriptase inhibitors, TIBO derivatives, QSAR

INTRODUCTION

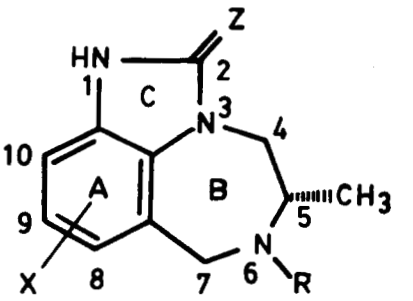
The human immunodeficiency virus (HIV) is a pathogenic retrovirus and causative agent of Acquired Immunodeficiency Syndrome (AIDS) and its related disorders. Despite advances in the therapy of some viral infections, little has been achieved in the area of chemotherapy of AIDS. This is mainly due to the fact that the retrovirus gets permanently integrated in the cellular chromosomes in the form of proviral DNA. However, a nucleoside analogue, 3′-azido-2′,3′-dideoxy thymidine (AZT or zidovudine) (**1**), was discovered[1] to inhibit the infectivity and cytopathicity of HIV-1, the most common form of HIV, at a very low concentration, and after many clinical studies and adequate trials, was approved for the treatment of HIV-1 infection. Unfortunately, it was found to suffer from a number of limitations including some side effects and the revelation of the possible emergence of drug resistance mutants of the virus.[2,3] After AZT, several other drugs were reported



(1)

to inhibit the infectivity and cytopathicity of HIV,[4] but their use was more restricted than AZT. Thus the need for new drugs to combat HIV infection is obvious.

So far the nucleoside analogues of which AZT and other recommended drugs are members have been prevalent. The common mechanism of action of these drugs therefore gives good reason to believe that all members of this structural class could suffer from some or all of the limitations of AZT. Thus clearly a need was felt that some other chemical families should be tried which may inhibit the HIV-1 virus possibly by alternative mechanisms. Consequently, some authors[5–9] focussed their attention on derivatives of 4,5,6,7-tetrahydro-5-methylimidazo [4,5,1-jk] [1,4] benzodiazepin-2(1H)-one (TIBO) (**2**). The mechanism of action of this series of drugs was found to be based on allosteric inhibition of viral reverse transcriptase leading to the retardation of viral replication.[10]



(2)

The initial structure-activity relationship (SAR) studies on TIBO derivatives were however directed to only alteration of the substituents at the various positions of the structure. Although these studies resulted into the discovery of a lead compound (**2**:Z=S,R=3,3-dimethylallyl, X=9–Cl), no rationale has yet been provided to reduce the trial and error factors. Hence, a quantitative SAR (QSAR) on these drugs was conducted since QSAR not only provides the rationale for drug design but also illuminates the mechanism of action of drugs.

MATERIALS AND METHODS

The QSAR analysis was made on TIBO derivatives studied by Kukla's group.[6–9] Their anti-HIV-1 data were compiled (Tables I–III) and subjected to multiple regression analysis using some physicochemical parameters. The most important physicochemical parameter was found to be the hydrophobic constant π. Its values were either taken directly from the literature[11] or calculated using the fragment constants.[11] Additionally, some dummy parameters were also used to describe the effect of some specific alterations.

All anti-HIV-1 data refer to the ability of compounds to inhibit the replication of the virus in MT-4 cells. It has been measured in terms of the IC_{50}, the minimum concentration of the compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of the virus.

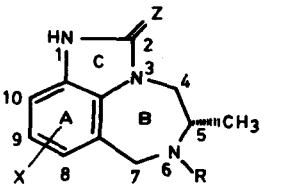
RESULTS AND DISCUSSIONS

Table I lists the compounds where a significant alteration in substituents was made at ring A of the TIBO (**2**).[9] In ring B, the substituent R was either DMA (3,3-dimethylallyl) or CPM (cyclopropylmethyl). Compound **30** is a lone compound where R=DEA (3,3-dimethylallyl). In ring C, the Z was replaced either by S or O. When a multiple regression analysis was performed, using a dummy parameter I_R for the R-substituent with a value of unity for R=DMA and zero for R=CPM or DEA and a dummy parameter I_Z for the Z-substituent with a value of unity for Z=S and zero for Z=O, and taking the hydrophobic constant of the X-substituents of ring A, a significant correlation was obtained as shown by the equation,

$$\log(1/IC_{50}) = 0.751(\pm 0.389)\pi_X + 1.250(\pm 0.574)I_Z + 0.601(\pm 0.769)I_R + 0.800(\pm 0.540)I_8 + 4.687$$

$$n = 34, r = 0.883, s = 0.70, F_{4,29} = 25.57 \quad (1)$$

TABLE I TIBO derivatives studied by Kukla *et al.*[9] and their anti-HIV-1 activity and physicochemical parameters

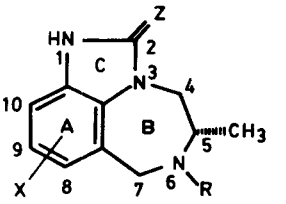


(2)

Compound No.	*X*	*Z*	*R*	π_X^a	log(1/IC$_{50}$)			
					Obsd.[b]	*Calcd.*		
						Eqn. (2)	*Eqn. (3)*	*Eqn. (5)*
1	H	S	DMA[c]	0.00	7.36	6.57	6.50	6.27
2	9-Cl	S	DMA	0.71	7.47	7.03	7.00	7.94
3	8-Cl	S	DMA	0.71	8.37	7.86	7.92	8.93
4	8-F	S	DMA	0.14	8.24	7.50	7.52	7.37
5	8-SCH_3	S	DMA	0.61	8.30	7.80	7.85	7.74
6	8-OCH_3	S	DMA	–0.02	7.47	7.40	7.41	7.25
7	8-OEt	S	DMA	0.38	7.02	7.65	7.69	7.56
8	8-CN	O	DMA	–0.57	5.94	5.73	5.65	5.60
9	8-CN	S	DMA	–0.57	7.25	7.05	7.03	6.81
10	8-CHO	S	DMA	0.65	6.73	7.00	6.98	6.75
11	8-$CONH_2$	O	DMA	–1.49	5.20	5.15	5.02	4.87
12	8-Br	O	DMA	0.86	7.33	6.65	6.65	6.73
13	8-Br	S	DMA	0.86	8.52	7.96	8.03	7.94
14	8-I	O	DMA	1.12	7.06	6.81	6.83	6.93
15	8-I	S	DMA	1.12	7.32	8.12	8.21	8.14
16	8-C≡CH	O	DMA	0.40	6.36	6.35	6.33	6.36
17	8-C≡CH	S	DMA	0.40	7.53	7.67	7.71	7.58
18	8-CH_3	O	DMA	0.56	6.00	6.46	6.44	6.49
19	8-CH_3	S	DMA	0.56	7.87	7.77	7.82	7.70
20	9-NO_2	O	CPM[d]	–0.28	4.48	4.23	4.08	4.13
21	8-NH_2	O	CPM	–1.23	3.07	4.47	4.36	4.37
22	8-$N(CH_3)_2$	O	CPM	0.18	5.18	5.36	5.33	5.49
23	9-NH_2	O	CPM	–1.23	4.22	3.63	3.42	3.38
24	9-$N(CH_3)_2$	O	CPM	0.18	5.18	4.52	4.40	4.49
25	9-$NHCOCH_3$	O	CPM	–0.97	3.80	3.79	3.61	3.59
26	9-NO_2	S	CPM	–0.28	5.61	5.54	5.46	5.34
27	9-F	S	DMA	0.14	7.60	6.66	6.59	6.38
28	9-CF_3	O	DMA	0.88	5.23	5.82	5.73	5.75
29	9-CF_3	S	DMA	0.88	6.31	7.13	7.11	6.96
30	9-CH_3	O	DEA[e]	0.56	6.50	–	4.67	4.79
31	10-OCH_3	O	DMA	–0.02	5.18	5.25	5.11	5.04
32	10-OCH_3	S	DMA	–0.02	5.33	6.56	6.48	6.25
33	9,10-diCl	S	DMA	1.42	7.60	7.48	7.48	7.39
34	10-Br	S	DMA	0.86	5.97	7.12	7.09	6.95

[a]Taken from Ref. 11. [b]Taken from Ref. 9. [c]3,3-Dimethylallyl. [d]Cyclopropylmethyl. [e]3,3-Diethylallyl.

TABLE II TIBO derivatives studied by Kukla *et al.*[6] and their anti-HIV-1 activity



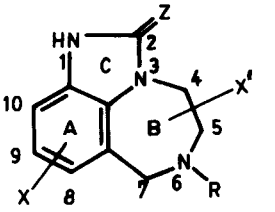
(2)

Compound No.	*X*	*Z*	*R*	log(1/IC_{50})		
				Obsd.[a]	*Calcd.*	
					Eqn. (3)	*Eqn. (5)*
1	H	O	$CH_2CH{=}CH_2$	4.15	4.28	4.35
2	H	O	2-MA[b]	4.33	4.28	4.35
3	H	O	$CH_2CO_2CH_3$	3.07	4.28	4.35
4	H	O	$CH_2C{\equiv}CH$	3.24	4.28	4.35
5	H	O	2-Furanyl methyl	3.97	4.28	4.35
6	H	O	$CH_2CH{=}CH_2$[S(+)]	4.18	4.28	4.35
7	H	O	$CH_2CH_2CH{=}CH_2$	4.30	4.28	4.35
8	H	O	$CH_2CH_2CH_3$	4.05	4.28	4.35
9	H	O	2-MA[S(+)]	4.72	4.28	4.35
10	H	O	CPM[c]	4.36	4.28	4.35
11	H	O	$CH_2CH{=}CHCH_3$(E)	4.24	4.28	4.35
12	H	O	$CH_2CH{=}CHCH_3$(Z)	4.46	4.28	4.35
13	H	O	$CH_2CH_2CH_2CH_3$	4.00	4.28	4.35
14	H	O	DMA[d]	4.90	5.12	5.06
15	H	O	$CH_2C(Br){=}CH_2$	4.21	4.28	4.35
16	H	O	$CH_2C(CH_3){=}CHCH_3$(E)	4.54	4.28	4.35
17	H	O	DMA [R(+)]	4.66	4.98	5.14
18	H	O	DMA [S(+)]	5.40	5.66	5.56
19	H	O	$CH_2C(C_2H_5){=}CH_2$	4.43	5.21	5.34
20	H	O	$CH_2CH{=}CHPh$(Z)	3.91	5.12	5.06
21	H	O	$CH_2C(CH{=}CH_2){=}CH_2$	4.15	4.28	5.46

[a]Taken from Ref. 6. [b]2-Methylallyl. [c]Cyclopropylmethyl. [d]3,3-Diethylallyl.

in which the additional parameter I_8 is also a dummy parameter used to account for the specific effect of the X-substituent at the 8-position. In this 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 are standard deviations. From the point of view of this last statistical parameter, the variable I_R does not appear to be significant, but when the lone compound **30** having R=DEA is deleted, this variable also becomes quite significant (Equation (2)).

TABLE III TIBO derivatives studied by Breslin *et al.*[8] and their anti-HIV-1 activity



Compound No.	*X*	*Z*	*R*	*X'*	log(1/IC_{50})		
					Obsd.[a]	*Calcd.*	
						Eqn. (4)	*Eqn. (5)*
1	8-Cl	S	DMA[b]	H	7.34	7.41	7.82
2	9-Cl	S	DMA	H	6.80	7.41	6.83
3	–	O	2-MA[c]	5,5-di-Me	4.64	4.52	4.35
4	–	O	2-MA	4-Me	4.50	4.52	4.35
5	9-Cl	S	2-MA	4-Me (*S*)	6.17	6.54	6.12
6	9-Cl	S	CPM[d]	4-Me (*R*)	5.66	6.54	6.12
7	–	O	n-Pr	4-i-Pr	4.13	4.52	4.35
8	–	O	2-MA	4-i-Pr	4.90	4.52	4.35
9	–	O	2-MA	4-n-Pr	4.32	4.52	4.35
10	–	O	DMA	7-Me	4.92	5.40	5.06
11	8-Cl	O	DMA	7-Me	6.84	6.22	6.61
12	9-Cl	O	DMA	7-Me	6.80	6.22	5.62
13	–	S	n-Pr	7-Me	5.61	5.71	5.56
14	–	S	DMA	7-Me	7.11	6.58	6.27
15	8-Cl	S	DMA	7-Me	7.92	7.41	7.82
16	9-Cl	S	DMA	7-Me	7.64	7.41	6.83
17	–	O	DMA	4,5-di-Me (cis)	4.25	4.60	5.06
18	–	S	DMA	4,5-di-Me (cis)	5.65	5.79	6.27
19	–	S	CPM	4,5-di-Me (trans)	4.87	4.91	5.56
20	–	S	DMA	4,5-di-Me (trans)	4.84	5.79	6.27
21	–	S	DMA	5,7-di-Me (trans)	7.38	5.79	6.27
22	–	S	DMA	5,7-di-Me (cis)	5.94	5.79	6.27
23	9-Cl	O	DMA	5,7-di-Me (*R*,*R*-trans)	6.64	5.43	5.62
24	9-Cl	S	DMA	5,7-di-Me (*R*,*R*-trans)	6.32	6.61	6.83
25	–	S	DMA	4,7-di-Me (trans)	4.59	5.79	6.27
26	9-Cl	S	DMA	5-Me (*S*)	7.47	8.26	7.94
27	8-Cl	S	DMA	5-Me (*S*)	8.37	8.26	8.94
28	9-Cl	O	DMA	5-Me (*S*)	6.74	7.08	6.73
29	9-Cl	S	CPM	5-Me (*S*)	7.47	7.39	7.23
30	–	S	CPM	5-Me (*S*)	7.22	6.58	6.67
31	–	O	n-Pr	5-Me	4.22	4.52	4.35
32	–	S	n-Pr	5-Me	5.78	5.71	5.56
33	–	O	2-MA	5-Me	4.46	4.52	4.35
34	–	S	DMA	5-Me	7.01	6.58	6.27
35	–	O	DMA	5-Me (*S*)	5.48	6.25	6.17
36	–	S	2-MA	5-Me (*S*)	7.59	6.58	6.67

[a]Taken from Ref. 8. [b]3,3-Dimethylallyl. [c]2-Methylallyl. [d]Cyclopropylmethyl.

$$\log(1/IC_{50}) = 0.635(\pm 0.375)\pi_X + 1.311(\pm 0.535)I_Z + 0.855(\pm 0.746)I_R + 0.837(\pm 0.502)I_8 + 4.408$$

$$n = 33, r = 0.904, s = 0.65, F_{4,28} = 31.20 \quad (2)$$

The deletion of this compound, in fact, leads to an overall improvement in the correlation. Now Equation (2) shows that a hydrophobic X-substituent will be beneficial to the activity and that it would be more beneficial if it is at the 8-position. Further, in ring C, Z=S is shown to be more advantageous than Z=O and a preference is revealed for a DMA group at the 6-position of ring B.

A slight variation in the substituents R at the 6-position was also studied[6] (Table II) and, although a noticeable correlation existing between the activity and calculated hydrophobic constant of R-substituents (described later) was noted, we could successfully combine these derivatives with those of Table I and obtained the equation,

$$\log(1/IC_{50}) = 0.694(\pm 0.324)\pi_X + 1.377(\pm 0.449)I_Z + 0.842(\pm 0.487)I_R + 0.930(\pm 0.421)I_8 + 4.279$$

$$n = 55, r = 0.925, s = 0.62, F_{4,50} = 73.74 \quad (3)$$

Since in this equation I_R is equal to 1 for DMA and zero for all other R-substituents, it suggests that DMA is the best suited substituent at the 6-position. Furthermore, since Equation (3) not only expresses a better correlation than Equation (1) but even better than Equation (2) which excludes compound **30** (no compound has been excluded in the derivation of Equation (3), the I_R seems to be the most suitable parameter to describe the effect of substituents at the 6-position.

The alterations at other positions of ring B were also examined[8] (Table III). When the data of Table III were analysed, we found that the 5-Me in the *S*-configuration was the most effective substituent but that disubstitution at any two different positions had a lowering effect (Equation (4)). In Equation (4), these two effects are described by the dummy parameters I_5 and D, respectively, with a value of 1 each. The I_X parameter in this equation has been used in place of π_X, as there were no variations in X-substituent. It was either Cl or H, which could be described by I_X with a value of unity for the former and zero for the latter.

$$\log(1/IC_{50}) = 0.829(\pm 0.531)I_X + 1.185(\pm 0.484)I_Z + 0.874(\pm 0.539)I_R + 0.851(\pm 0.600)I_5 - 0.795(\pm 0.631)D + 4.521$$

$$n = 36, r = 0.877, s = 0.65, F_{5,30} = 20.08 \quad (4)$$

However, this series of derivatives could also be beautifully combined with those of Tables I and II without any appreciable loss in the significance of the correlation (Equation (5)). This shows the validity of all our correlations. For such a large series of compounds, Equation (5) is capable of accounting for 81% of the variance in the activity ($r^2 = 0.81$). Its F-value is highly significant at 99% level [$F_{5,83}(0.01) = 3.22$] and so is the case for Equations (2) and (3) [$F_{4,28}(0.01) = 4.07$; $F_{4,50}(0.01) = 3.72$]. In the combined series, the parameter D was found to be of little significance.

$$\log(1/\mathrm{IC}_{50}) = 0.789(\pm 0.297)\pi_X + 1.212(\pm 0.308)I_Z + 0.991(\pm 0.350)I_8 + 0.706(\pm 0.337)I_R + 1.109(\pm 0.518)I_5 + 4.352$$
$$n = 89, r = 0.900, s = 0.65, F_{5,83} = 70.57 \quad (5)$$

In the derivation of Equation (5) compounds **26** and **27** of Table III were not included as they are identical to compounds **2** and **3** of Table I, respectively. The successive development of this equation is described in Table IV and that the variables used have no mutual correlations is shown in Table V. The following conclusions can now be drawn from these correlation studies.

(1) A highly hydrophobic substituent in ring A, particularly at its 8-position, would be the most favourable to the activity. The substituents in this ring are indicated to have strong hydrophobic interaction with the receptor, the enzyme viral reverse transcriptase (VRT).

TABLE IV Successive development of correlations for the combined group of compounds ($n = 89$)

Eqn. No.	*Equation*	r	s	F
1	$\log(1/\mathrm{IC}_{50}) = 1.463(\pm 0.513)\pi_X + 5.468$	0.520	1.23	32.20
2	$\log(1/\mathrm{IC}_{50}) = 1.032(\pm 0.400)\pi_X + 1.684(\pm 0.408)I_Z + 4.787$	0.769	0.93	62.15
3	$\log(1/\mathrm{IC}_{50}) = 0.991(\pm 0.334)\pi_X + 1.553(\pm 0.343)I_Z + 1.174(\pm 0.377)I_8 + 4.550$	0.847	0.78	72.19
4	$\log(1/\mathrm{IC}_{50}) = 0.840(\pm 0.323)\pi_X + 1.350(\pm 0.339)I_Z + 0.903(\pm 0.383)I_8 + 0.685(\pm 0.375)I_R + 4.376$	0.870	0.73	65.25
5	$\log(1/\mathrm{IC}_{50}) = 0.888(\pm 0.290)\pi_X + 1.330(\pm 0.306)I_Z + 0.958(\pm 0.334)I_8 + 0.619(\pm 0.222)\pi_R + 3.473$	0.891	0.67	80.65
6	$\log(1/\mathrm{IC}_{50}) = 0.789(\pm 0.297)\pi_X + 1.212(\pm 0.308)I_Z + 0.991(\pm 0.350)I_8 + 0.706(\pm 0.337)I_R + 1.109(\pm 0.518)I_5 + 4.352$	0.900	0.65	70.57
7	$\log(1/\mathrm{IC}_{50}) = 0.807(\pm 0.280)\pi_X + 1.263(\pm 0.286)I_Z + 1.050(\pm 0.321)I_8 + 0.703(\pm 0.271)\pi_R + 1.080(\pm 0.495)I_5 + 3.187$	0.909	0.62	78.67

TABLE V Mutual correlations (r-values) of the variables used in deriving Equation (5).

	π_X	I_Z	I_8	I_R	I_5
π_X	1.0	0.294	0.097	0.348	0.141
I_Z		1.0	0.176	0.407	0.163
I_8			1.0	0.425	0.071
I_R				1.0	0.019
I_5					1.0

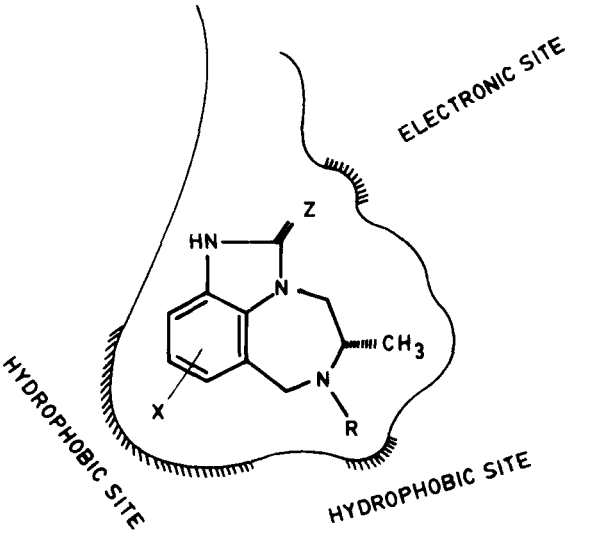


FIGURE 1 The proposed model for the interaction of TIBO derivatives with the receptor.

(2) At position 2, the sulfur leads to better activity than the oxygen. It may be assumed that both the sulfur and the oxygen may be involved in some charge-transfer phenomenon with the receptor, in which the former may act as a better electron donor than the latter since its ionization potential (999 kJ/mole) is much lower than that of oxygen (1410 kJ/mole).

(3) Among the R-substituents at position 6, the 3,3-dimethylallyl (DMA) is found to be the best. The R-substituents may be assumed to have a hydrophobic interaction with the receptor in which the DMA may be expected to possess the optimum hydrophobicity. We had attempted to correlate the activity

of compounds in Table II with the calculated hydrophobic constant of the R-substituents and obtained a linear correlation with $r = 0.70$. It was however observed that the low activity of compound **20** did not corroborate to the highest π value of this compound in the series. On removing this compound, an improved correlation was obtained with $r = 0.85$. However, in the combined series, the hydrophobic parameter π_R had hardly any better significance than the dummy parameter I_R used for DMA (compare, in Table IV, Equation (4) with (5) and Equation (6) with (7)).

(4) The 5-Me in the *S*-configuration was the most suited substituent in ring B. This group in this configuration probably has the best access to the receptor.

Based on the above conclusions, a model as shown in Figure 1 is proposed for the binding of the TIBO derivatives with the receptor.

Acknowledgements

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