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Hydrophobic, topological and steric parameter based QSAR study on peptidic HIV-protease inhibitors

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ABSTRACT

Anti-HIV drug discovery has been increasingly focusing on HIV-protease as a potential therapeutic target. QSAR study of three sets of peptidic HIV-protease inhibitors has been studied. The descriptor that have been used are log P for the measurement of pharmacokinetics, topological indices (chi0v and chi1v and KierA1) for the molecular structure quantization, and steric parameters (MR and MW) for the measurement of electronic effect and dipole-dipole interaction at the active site. The values of descriptors that have been used for QSAR models have been evaluated by CAChe software using the by PM3 method. The relationship between various descriptors and inhibitory activity has been presented. The combination of descriptors that provide best QSAR model and have correlation coefficient value above 0.80 is log P, chi1v, KierA1 and MR. The compounds having higher inhibitory activity have been identified on the basis of pharmacokinetics.

KEYWORDS

Protease inhibitor;
QSAR;
PM3;
Pharmacokinetics.

INTRODUCTION

Anti-HIV drug discovery has been increasingly focusing on HIV-protease as a potential therapeutic target[1-3]. Since HIV-protease is an aspartic protease and its substrate is peptide in nature, a number of peptide derived compounds have been identified as HIV-protease inhibitors[4]. These peptidic HIV-protease inhibitors bind to the substrate binding site pocket of the enzyme that has a considerable number of hydrophobic residues[5-7]. The amino acids that make up these pockets are Valine-32, Isoleucine-47, Isoleucine-50 and Isoleucine-84 in each monomer of homodimeric polypeptides of the HIV-protease. Isoleucine and valine have their hydropathy index 4.5 and 4.2 and are the top hydrophobic amino acids respectively. According to Huff[8], the inhibitor-enzyme binding is dominated by hydrophobic interaction. Hence the inhibitors must have higher hydrophobicity[9] for strong and effective hydrophobic interaction with hydrophobic amino acids of the binding pocket. Although, the activity of inhibitors increases as their hydrophobicity (log P) increases but log P above 5.0 show poor pharmacokinetics[10], including low oral bioavailability and rapid excretion. Since, the pharmacokinetics of a drug is as important to its efficacy as is its pharmacodynamics, both must be optimized in producing a medicinally useful drug. One of the most important empirically based rule[11] formulated by Chris-

topher Lipinski is that a compound is likely to exhibit poor absorption or permeation if its value of log P is greater than 5.0. Thus, the most effective drugs are usually a compromise; they are neither too hydrophobic nor too hydrophilic. Recently, QSAR[12,13] has gained importance in the field of pharmacological sciences. In this paper we present QSARstudy of three sets of peptidic HIV-protease inhibitors from the literature[14,15] with the help of following descriptors:

(i). Log P for the measurement of pharmacokinetics,

(ii). Topological indices (chi0v and chi1v and KierA1) for the molecular structure quantization, and

(iii). Steric parameters (MR and MW) for the measurement of electronic effect and dipole-dipole interaction at the active site.

THEORY

If the hydrophobicity of a drug is important for its biological activity, then changing the substituents on the drug so as to alter its hydrophobicity will affect its activity. Of course, the biological activities of these drugs (peptidic HIV-protease inhibitors) depend on their hydrophobicities. A measure of the drug's hydrophobicity is its partition coefficient (P) between two immiscible solvents, octanol and water at equilibrium[16,17]:

$$\text{Log } P = \log\left[\frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in water}}\right] \quad (1)$$

Biological activity may be expressed as 1/C, where C is the drug concentration required to achieve a specified level of biological function and can be expressed:

$$\text{Log}(1/C) = k_1 \log P + k_2 \quad (2)$$

here k_1 and k_2 are constants, where optimum values in this QSAR can be determined by computerized curve-fitting methods.

For compounds with a larger range of log P values it is better described by quadratic equation:

$$\text{Log}(1/C) = k_1 (\log P)2 + k_2 \log P + k_3 \quad (3)$$

The topological indices are molecular connectivity indices and shape index. Molecular connectivity is a method of molecular structure quantization in which weighted counts of substructure fragments are incorporated into numerical indices such as size, branching, unsaturation, hetero atom content and cyclicity which are encoded. Substructures for molecular skeleton are defined by the decomposition of the skeleton into fragments of atom (zero order, m=0) and one bond paths (first order, m=1). The calculation of the indices begins with the reduction of the molecule to hydrogen-suppressed skeleton. The molecular connectivity indices are symbolized by ${}^{m}X_t$. The valence connectivity index[18] of zero (chi0v = ${}^{0}\chi_t^{v}$) and first order (chi1v = ${}^{1}\chi_t^{v}$) is given respectively by eqn-4 and eqn-5

$${}^{0}\chi_t^{v} = \sum_{i=1}^{Ns} {}^{0}C_i^{v} \quad (4)$$

$${}^{0}\chi_t^{v} = \sum_{i=1}^{Ns} {}^{1}C_i^{v} \quad (5)$$

where ${}^{0}Ci^{v}$ and ${}^{1}Ci^{v}$ are given by eqn-6 and eqn-7

$${}^{0}C_i^{v} = \prod_{k=1}^{m+1} (\delta_k{}^{v})^{-0.5} \quad (6)$$

$${}^{1}C_i^{v} = \prod_{k=1}^{m+1} (\delta_k{}^{v})^{-0.5} \quad (7)$$

The Kappa shape indices[19] (${}^{m}K$) are also a method of molecular structure quantization in which attributes of molecular shape are encoded into kappa values(${}^{1}K$ for first order, ${}^{2}K$for second order, ${}^{3}K$ for third order, ${}^{1}K\alpha$ for kappa alfa first order). The values of the kappa alpha, order 1(KierA1 = ${}^{1}K\alpha$) can be calculated directly from the equation-.

$${}^{1}K\alpha = \frac{(A+\alpha)[(A+\alpha)-1]^2}{({}^{1}Pi+\alpha)^2} \quad (8)$$

where α is given by

$$\alpha = r(x)/r[C(sp^3)] - 1 \quad (9)$$

here r(x) is the covalent radius of atom x and r[C(sp^3)] is the covalent radius of carbon in sp^3 state.

Molecular refractivity (MR) is used as a steric parameter[20] and measures the electronic effect also and may reflect the dipole-dipole interaction at the active site,

$$MR = \frac{[(n^2-1)/(n^2+2)]MW}{d} \quad (10)$$

where n is the refractive index for the sodium D line, MW is the molecular weight and d is the density of the compound. Molecular weight (MW) is also used as steric parameter.

Full Paper

TABLE 1: First set of derivatives containing 15 compounds and their biological activity in terms of inhibitory activity

Comp. no.	Substituents R	X	Y	Z	Inhibitory activity(A)
1	Cbz	H	$CHMe_2$	Me	5.82
2	Qua	H	$CHMe_2$	n-Bu	6.90
3	Cbz	H	$CHMe_2$	n-Pr	6.29
4	Cbz	H	$CHMe_2$	Et	6.48
5	Cbz	H	$CHMe_2$	i-Pr	6.59
6	Cbz	H	$CHMe_2$	t-Bu	7.46
7	Qua	H	$CHMe_2$	t-Bu	8.22
8	Cbz	H	CH_2CHMe_2	t-Bu	7.89
9	Qua	H	CH_2CHMe_2	t-Bu	8.52
10	Cbz	H	C_6H_{11}	t-Bu	7.54
11	Qua	H	C_6H_{11}	t-Bu	8.30
12	Cbz	H	C_6H_5	t-Bu	7.72
13	Qua	H	C_6H_5	t-Bu	8.52
14	Cbz	H	4-Py	t-Bu	6.98
15	Qua	H	4-Py	t-Bu	7.72

Cbz= Carbobenzyloxy, Qua=Quinolinyl-2-Carboxamide

TABLE 2: Second set of derivatives containing 15 compounds and their biological activity in terms of inhibitory activity

Comp. no.	Substituents R_1	R2	R3	Inhibitory activity(A)
16	CH_2Ph	H	H	9.60
17	CH_2Ph	Me	H	8.11
18	CH_2CH_2Ph	H	OH	9.72
19	CH_2-4-CF_3Ph	H	H	9.59
20	(E)CH_2CH=CHPh	H	H	9.64
21	$CH_2C_6F_5$	H	H	9.22
22	CH_2-4-CH_3Ph	H	H	9.54
23	CH_2-4-NH_2Ph	H	H	9.51
24	CH_2-4-NO_2Ph	H	H	9.57
25	CH_2-4-OHPh	H	H	9.80
26	$CH_2CH=CH_2$	H	H	7.56
27	CH_2-4-IPh	H	H	9.14
28	$CH_2C(O)Ph$	H	H	8.27
29	CH_2SPh	H	H	9.60
30	CH_2-4-CMe_3Ph	H	H	9.77

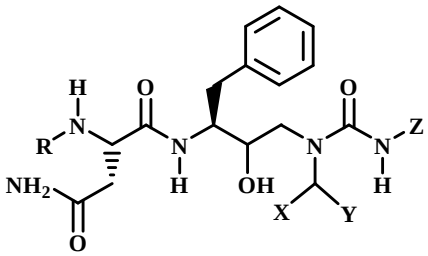

Figure 1: Skeleton structure of parent compound of first set

TABLE 3: Third set of derivatives containing 11 compounds and their biological activity in terms of inhibitory activity

Comp. no.	Substituents (X)	Inhibitory activity(A)
31	Ph CH_2NH-	6.94
32	HO-C_5H_6-NH-	7.47
33	Ph CH_2-CH(CH_3OH)NH-	6.16
34	HOOC-CH(i-pr)NH-	6.79
35	MeOOC-C_9H_8-NH-	7.18
36	HO-C_9H_7(Me)NH-	6.67
37	HO-C_6H_{10}-NH-	6.91
38	HO-C_9H_8O-NH-	7.39
39	C_9H_9-NH-	6.89
40	C_6H_{11}-CH(Me)NH-	6.84
41	Ph-CH(CH_2OH)NH-	7.41

TABLE 4.1 : Relationship between log P and activity of compounds of first set

Comp. no.	Substituents R	X	Y	Z	Inhibitory activity(A)	Log P
Subgroup-A						
1	Cbz	H	$CHMe_2$	Me	5.82	1.558
4	Cbz	H	$CHMe_2$	Et	6.48	1.901
5	Cbz	H	$CHMe_2$	i-Pr	6.59	2.314
12	Cbz	H	C_6H_5	t-Bu	7.72	2.908
9	Qua	H	CH_2CHMe_2	t-Bu	8.52	3.077
Subgroup-B						
14	Cbz	H	4-Py	t-Bu	6.98	1.643
6	Cbz	H	$CHMe_2$	t-Bu	7.46	2.392
8	Cbz	H	CH_2CHMe_2	t-Bu	7.89	2.716
11	Qua	H	C_6H_{11}	t-Bu	8.30	3.359
Subgroup-C						
3	Cbz	H	$CHMe_2$	n-Pr	6.29	2.369
2	Qua	H	$CHMe_2$	n-Bu	6.90	2.922
10	Cbz	H	C_6H_{11}	t-Bu	7.54	3.72
7*	Qua	H	CHMe2	t-Bu	8.22	2.549
15*	Qua	H	4-Py	t-Bu	7.72	1.664
13*	Qua	H	C6H5	t-Bu	8.52	2.07

Cbz = Carbobenzyloxy, Qua=Quinolinyl-2-Carboxamide

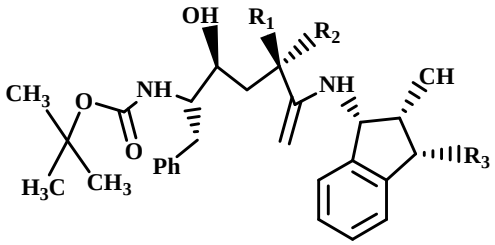

Figure 2: Skeleton structure of parent compound of second set

RESULT AND DISCUSSION

Since the skeleton structures of parent compound (Figures 1-3) are different, the peptidic HIV-protease inhibitors have been divided in three sets, which along with their biological activity are presented in TABLES

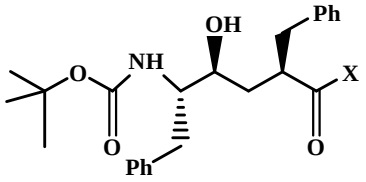

Figure 3: Skeleton structure of parent compound of third set

TABLE 4.2 : Relationship between chi0v and activity of compounds of first set

Comp. no.	Substituents R	X	Y	Z	Inhibitory activity(A)	chi0v
Subgroup -A						
1	Cbz	H	$CHMe_2$	Me	5.82	22.631
4	Cbz	H	$CHMe_2$	Et	6.48	23.339
5	Cbz	H	$CHMe_2$	i-Pr	6.59	24.209
14	Cbz	H	4-Py	t-Bu	6.98	25.811
8	Cbz	H	CH_2CHMe_2	t-Bu	7.89	25.839
7	Qua	H	$CHMe_2$	t-Bu	8.22	26.449
9	Qua	H	CH_2CHMe_2	t-Bu	8.52	26.667
13	Qua	H	C_6H_5	t-Bu	8.52	27.258
Subgroup -B						
3	Cbz	H	$CHMe_2$	n-Pr	6.29	24.046
6	Cbz	H	$CHMe_2$	t-Bu	7.46	25.131
10	Cbz	H	C_6H_{11}	t-Bu	7.54	27.156
15	Qua	H	4-Py	t-Bu	7.72	28.018
11	Qua	H	C_6H_{11}	t-Bu	8.30	28.277
2*	Qua	H	$CHMe_2$	n-Bu	6.90	26.07
12*	Cbz	H	C_6H_5	t-Bu	7.72	27.013

Cbz= Carbobenzyloxy, Qua=Quinolinyl-2-Carboxamide, chi0v = valence connectivity index of zero order

TABLE 4.3: Relationship between chi1v and activity of compounds of first set

Comp. no.	Substituents R	X	Y	Z	Inhibitory activity(A)	chi1v
Subgroup-A						
1	Cbz	H	$CHMe_2$	Me	5.82	18.583
4	Cbz	H	$CHMe_2$	Et	6.48	19.083
5	Cbz	H	$CHMe_2$	i-Pr	6.59	19.438
6	Cbz	H	$CHMe_2$	t-Bu	7.46	19.729
8	Cbz	H	CH_2CHMe_2	t-Bu	7.89	20.229
7	Qua	H	$CHMe_2$	t-Bu	8.22	21.212
9	Qua	H	CH_2CHMe_2	t-Bu	8.52	21.391
13	Qua	H	C_6H_5	t-Bu	8.52	23.036
Subgroup-B						
3	Cbz	H	$CHMe_2$	n-Pr	6.29	19.583
14	Cbz	H	4-Py	t-Bu	6.98	21.391
10	Cbz	H	C_6H_{11}	t-Bu	7.54	21.802
11	Qua	H	C_6H_{11}	t-Bu	8.30	22.874
2*	Qua	H	$CHMe_2$	n-Bu	6.90	21.566
12*	Cbz	H	C_6H_5	t-Bu	7.72	21.415
15*	Qua	H	4-Py	t-Bu	7.72	23.514

Cbz= Carbobenzyloxy, Qua=Quinolinyl-2-Carboxamide, chi1v = valence connectivity index of first order

TABLE 4.4 : Relationship between KierA1and activity of compounds of first set

Comp. no.	Substituents R	X	Y	Z	Inhibitory activity(A)	KierA1
Subgroup-A						
1	Cbz	H	$CHMe_2$	Me	5.82	32.054
4	Cbz	H	$CHMe_2$	Et	6.48	33.049
5	Cbz	H	$CHMe_2$	i-Pr	6.59	34.043
6	Cbz	H	$CHMe_2$	t-Bu	7.46	35.038
10	Cbz	H	C_6H_{11}	t-Bu	7.54	35.268
8	Cbz	H	CH_2CHMe_2	t-Bu	7.89	36.033
9	Qua	H	CH_2CHMe_2	t-Bu	8.52	36.31
Subgroup-B						
12	Cbz	H	C_6H_5	t-Bu	7.72	32.038
15	Qua	H	4-Py	t-Bu	7.72	32.21
7	Qua	H	CHMe2	t-Bu	8.22	35.726
11	Qua	H	C_6H_{11}	t-Bu	8.30	37.075
13*	Qua	H	C_6H_5	t-Bu	8.52	32.599
3*	Cbz	H	$CHMe_2$	n-Pr	6.29	34.043
14*	Cbz	H	4-Py	t-Bu	6.98	35.469
2*	Qua	H	$CHMe_2$	n-Bu	6.90	35.726

Cbz= Carbobenzyloxy, Qua=Quinolinyl-2-Carboxamide, KierA1 = kappa alfa first order

TABLE 4.5 : Relationship between MR and activity of compounds of first set

Comp. no.	Substituents R	X	Y	Z	Inhibitory activity(A)	MR
Subgroup-A						
1	Cbz	H	$CHMe_2$	Me	5.82	142.697
4	Cbz	H	$CHMe_2$	Et	6.48	147.445
5	Cbz	H	$CHMe_2$	i-Pr	6.59	151.864
6	Cbz	H	$CHMe_2$	t-Bu	7.46	156.501
10	Cbz	H	C_6H_{11}	t-Bu	7.54	167.485
15	Qua	H	4-Py	t-Bu	7.72	170.662
11	Qua	H	C_6H_{11}	t-Bu	8.30	171.945
13	Qua	H	C_6H_5	t-Bu	8.52	180.764
Subgroup-B						
3	Cbz	H	$CHMe_2$	n-Pr	6.29	151.97
8	Cbz	H	CH_2CHMe_2	t-Bu	7.89	161.179
7	Qua	H	$CHMe_2$	t-Bu	8.22	165.873
9	Qua	H	CH_2CHMe_2	t-Bu	8.52	168.502
12*	Cbz	H	C_6H_5	t-Bu	7.72	147.974
14*	Cbz	H	4-Py	t-Bu	6.98	165.213
2*	Qua	H	$CHMe_2$	n-Bu	6.90	165.943

Cbz= Carbobenzyloxy, Qua=Quinolinyl-2-Carboxamide, MR = molar refractivity

1-3. The reactivity indices, Log P, chi0v, chi1v, KierA1, MR and MW of the corresponding derivatives are presented in TABLES 4.1-4.6 for first set; in TABLES 5.1-5.6 for second set and in TABLES 6.1-6.6 for third set. Each table has been divided into subgroups in order to demonstrate better sequential relationship between the biological activity and the reactivity indices. The QSAR study of each set is presented below

TABLE 4.6: Relationship between MW and activity of compounds of first set

Comp. no.	Substituents R	X	Y	Z	Inhibitory activity(A)	MW
Subgroup-A						
1	Cbz	H	$CHMe_2$	Me	5.82	541.646
4	Cbz	H	$CHMe_2$	Et	6.48	555.673
5	Cbz	H	$CHMe_2$	i-Pr	6.59	569.7
6	Cbz	H	$CHMe_2$	t-Bu	7.46	583.726
8	Cbz	H	CH_2CHMe_2	t-Bu	7.89	597.753
7	Qua	H	$CHMe_2$	t-Bu	8.22	620.747
9	Qua	H	CH_2CHMe_2	t-Bu	8.52	623.791
13*	Qua	H	C_6H_5	t-Bu	8.52	654.764
Subgroup-B						
3	Cbz	H	$CHMe_2$	n-Pr	6.29	569.7
14	Cbz	H	4-Py	t-Bu	6.98	618.731
2	Qua	H	$CHMe_2$	n-Bu	6.90	620.747
12	Cbz	H	C_6H_5	t-Bu	7.72	623.791
11	Qua	H	C_6H_{11}	t-Bu	8.30	660.812
10*	Cbz	H	C_6H_{11}	t-Bu	7.54	634.774
15*	Qua	H	4-Py	t-Bu	7.72	669.779

Cbz= Carbobenzyloxy, Qua=Quinolinyl-2-Carboxamide, MW = molecular weight

TABLE 5.1: Relationship between Log P and activity of compounds of second set

Comp. no.	Substituents R_1	R2	R3	Inhibitory activity(A)	Log P
Subgroup-A					
26	$CH_2CH=CH_2$	H	H	7.56	4.352
17	CH_2Ph	Me	H	8.11	4.994
23	CH_2-4-NH_2Ph	H	H	9.51	4.605
22	CH_2-4-CH_3Ph	H	H	9.54	5.855
19	CH_2-4-CF_3Ph	H	H	9.59	6.271
20	(E)$CH_2CH=CHPh$	H	H	9.64	6.317
30	CH_2-4-CMe_3Ph	H	H	9.77	7.015
16*	CH_2Ph	H	H	9.60	5.388
Subgroup-B					
25	CH_2-4-OHPh	H	H	9.80	5.104
29	CH_2SPh	H	H	9.60	5.175
24	CH_2-4-NO_2Ph	H	H	9.57	5.436
21	$CH_2C_6F_5$	H	H	9.22	6.086
27	CH_2-4-IPh	H	H	9.14	6.646
18*	CH_2CH_2Ph	H	OH	9.72	5.784
28*	$CH_2C(O)Ph$	H	H	8.27	4.461

First set

The first set consists of fifteen urea isostere derivatives and their biological activity has been measured in terms of inhibitory activity[14].

The values of reactivity indices, log P; chi0v; chi1v; KherA1; MR and MW, of this set of compounds alongwith their reported inhibitory activity are placed in TABLES 4.1-4.6 respectively. A close look at the TABLES indicates that successive addition of

TABLE 5.2: Relationship between chi0v and activity of compounds of second set

Comp. no.	Substituents R_1	R2	R3	Inhibitory activity(A)	chi0v
Subgroup -A					
26	$CH_2CH=CH_2$	H	H	7.56	21.315
23	CH_2-4-NH_2Ph	H	H	9.51	23.917
22	CH_2-4-CH_3Ph	H	H	9.54	24.340
24	CH_2-4-NO_2Ph	H	H	9.57	24.604
29	CH_2SPh	H	H	9.60	24.642
20	(E)$CH_2CH=CHPh$	H	H	9.64	25.279
30	CH_2-4-CMe_3Ph	H	H	9.77	26.84
Subgroup -B					
25	CH_2-4-OHPh	H	H	9.80	23.787
18	CH_2CH_2Ph	H	OH	9.72	24.124
28	$CH_2C(O)Ph$	H	H	8.27	24.326
17	CH_2Ph	Me	H	8.11	24.522
Subgroup -C					
16	CH_2Ph	H	H	9.60	23.417
19	CH_2-4-CF_3Ph	H	H	9.59	24.974
27	CH_2-4-IPh	H	H	9.14	25.875
21*	$CH_2C_6F_5$	H	H	9.22	24.920

chi0v = valence connectivity index of zero order

TABLE 5.3: Relationship between chi1v and activity of compounds of second set

Comp. no.	Substituents R_1	R2	R3	Inhibitory activity(A)	chi1v
Subgroup -A					
26	$CH_2CH=CH_2$	H	H	7.56	17.069
17	CH_2Ph	Me	H	8.11	19.432
27	CH_2-4-IPh	H	H	9.14	19.480
23	CH_2-4-NH_2Ph	H	H	9.51	19.480
22	CH_2-4-CH_3Ph	H	H	9.54	19.480
24	CH_2-4-NO_2Ph	H	H	9.57	20.518
19	CH_2-4-CF_3Ph	H	H	9.59	20.692
30*	CH_2-4-CMe_3Ph	H	H	9.77	20.692
Subgroup -B					
25	CH_2-4-OHPh	H	H	9.80	19.480
18	CH_2CH_2Ph	H	OH	9.72	19.586
29	CH_2SPh	H	H	9.60	19.586
28	$CH_2C(O)Ph$	H	H	8.27	19.997
20*	(E)$CH_2CH=CHPh$	H	H	9.64	20.586
21*	$CH_2C_6F_5$	H	H	9.22	21.157
16*	CH2Ph	H	H	9.60	19.086

chi1v = valence connectivity index of first order

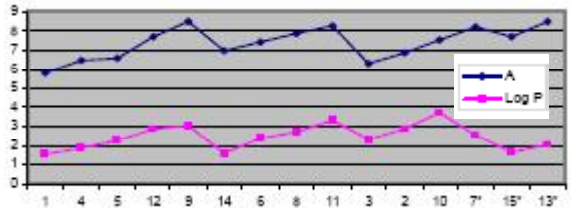

Figure 4: Graphic representation of relationship between Log P and Activity of compounds of first set

subsititutents Me, Et, i-Pr, t-Bu, 4-Py, CHMe2,

TABLE 5.4: Relationship between KierA1 and activity of compounds of second set

Comp. no.	Substituents R_1	R2	R3	Inhibitory activity(A)	KierA1
Subgroup-A					
26	$CH_2CH=CH_2$	H	H	7.56	27.900
23	CH_2-4-NH_2Ph	H	H	9.51	30.712
22	CH_2-4-CH_3Ph	H	H	9.54	30.752
24	CH_2-4-NO_2Ph	H	H	9.57	32.278
19	CH_2-4-CF_3Ph	H	H	9.59	33.482
30	CH_2-4-CMe_3Ph	H	H	9.77	33.688
Subgroup-B					
17	CH_2Ph	Me	H	8.11	30.918
28	$CH_2C(O)$Ph	H	H	8.27	31.407
27	CH_2-4-IPh	H	H	9.14	31.465
21	$CH_2C_6F_5$	H	H	9.22	34.326
Subgroup-C					
16	CH_2Ph	H	H	9.60	29.775
29	CH_2SPh	H	H	9.60	31.094
20	(E)$CH_2CH=CH$Ph	H	H	9.64	32.454
18*	CH_2CH_2Ph	H	OH	9.72	30.752
25*	CH_2-4-OHPh	H	H	9.80	30.712

KierA1 = kappa alfa first order

TABLE 5.5: Relationship between MR and activity of compounds of second set

Comp. no.	Substituents R_1	R2	R3	Inhibitory activity(A)	MR
Subgroup -A					
21	$CH_2C_6F_5$	H	H	9.22	155.954
23	CH_2-4-NH_2Ph	H	H	9.51	159.573
22	CH_2-4-CH_3Ph	H	H	9.54	159.914
24	CH_2-4-NO_2Ph	H	H	9.57	161.796
29	CH_2SPh	H	H	9.60	162.654
20	(E)$CH_2CH=CH$Ph	H	H	9.64	169.792
Subgroup -B					
26	$CH_2CH=CH_2$	H	H	7.56	139.423
17	CH_2Ph	Me	H	8.11	160.050
28	$CH_2C(O)$Ph	H	H	8.27	160.260
27	CH_2-4-IPh	H	H	9.14	167.281
Subgroup -C					
16	CH_2Ph	H	H	9.60	154.872
18	CH_2CH_2Ph	H	OH	9.72	159.473
30	CH_2-4-CMe_3Ph	H	H	9.77	173.538
25*	CH_2-4-OHPh	H	H	9.80	156.567
19*	CH_2-4-CF_3Ph	H	H	9.59	160.846

MR = molar refractivity

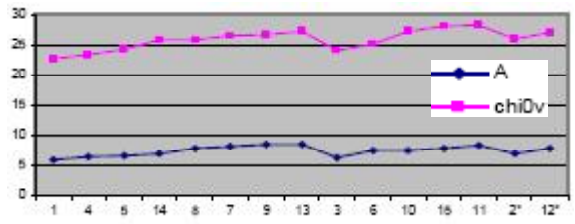

Figure 5: Graphic representation of relationship between chi0v and Activity of compounds of first set

TABLE 5.6 : Relationship between MW and activity of compounds of second set

Comp. no.	Substituents R_1	R2	R3	Inhibitory activity(A)	MW
Subgroup-A					
26	$CH_2CH=CH_2$	H	H	7.56	494.630
17	CH_2Ph	Me	H	8.11	558.716
22	CH_2-4-CH_3Ph	H	H	9.54	558.716
18	CH_2CH_2Ph	H	OH	9.72	558.716
25	CH_2-4-OHPh	H	H	9.80	560.689
Subgroup-B					
27	CH_2-4-IPh	H	H	9.14	670.585
21	$CH_2C_6F_5$	H	H	9.22	634.642
19	CH_2-4-CF_3Ph	H	H	9.59	612.688
30	CH_2-4-CMe_3Ph	H	H	9.77	600.797
Subgroup-C					
28	$CH_2C(O)$Ph	H	H	8.27	572.700
29	CH_2SPh	H	H	9.60	576.749
20	(E)$CH_2CH=CH$Ph	H	H	9.64	584.754
23*	CH_2-4-NH_2Ph	H	H	9.51	559.704
24*	CH_2-4-NO_2Ph	H	H	9.57	589.687
16*	CH_2Ph	H	H	9.60	544.689

MW = molecular weight

CH2CHMe2, carbobenzyloxy and quinolinyl-2-carboxamide increases the hydrophobicity and also the inhibitory activity. The relationship is well demonstrated by graph (Figures 4-6) drawn between the inhibitory activity and reactivity indices. Although there is a direct relationship but there is no sequential rise or fall. In order to provide sequential relationship we have divided the TABLES 4.1-4.6 into subgroups: TABLE 4.1 into three subgroups-A, B, and C; while TABLES 4.2-4.6 into two subgroups-A and B. The compounds in each subgroup show the sequential relationship very clearly. Compounds which do not follow the sequential trend are indicated by *.

Second set

Second set of isostere derivatives also contains fifteen compounds and their biological activity is also shown in term of inhibitory activity[15].

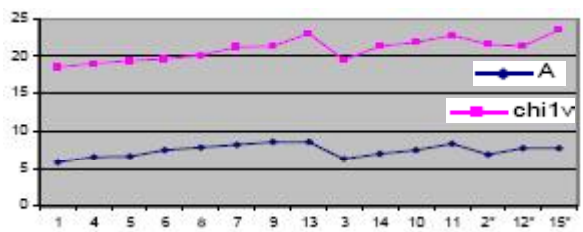

Figure 6 : Graphic representation of relationship between chi1v and Activity of compounds of first set

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TABLE 6.1: Relationship between log P and activity of compounds of third set

Comp. no.	Substituents(X)	Inhibitory activity(A)	Log P
Subgroup-A			
33	Ph CH_2-CH(CH_3OH)NH-	6.16	3.489
36	HO-C_9H_7(Me)NH-	6.67	3.367
34	HOOC-CH(i-pr)NH-	6.79	2.784
37	HO-C_6H_{10}-NH-	6.91	2.649
Subgroup-B			
40	C_6H_{11}-CH(Me)NH-	6.84	4.145
39	C_9H_9-NH-	6.89	3.913
38	HO-C_9H_8O-NH-	7.39	3.732
41	Ph-CH(CH_2OH)NH-	7.41	3.359
35*	MeOOC-C_9H_8-NH-	7.18	4.080
31*	Ph CH_2NH-	6.94	3.609
32*	HO-C_5H_6-NH-	7.47	4.058

TABLE 6.2: Relationship between chi0v and Activity of compounds of third set

Comp. no.	Substituents (X)	Inhibitory activity(A)	chi0v
Subgroup-A			
33	Ph CH_2-CH(CH_3OH)NH-	6.16	19.66
34	HOOC-CH(i-pr)NH-	6.79	18.345
37	HO-C_6H_{10}-NH-	6.91	18.265
31	Ph CH_2NH-	6.94	17.929
Subgroup-B			
36	HO-C_9H_7(Me)NH-	6.67	20.376
40	C_6H_{11}-CH(Me)NH-	6.84	19.525
39	C_9H_9-NH-	6.89	19.136
38	HO-C_9H_8O-NH-	7.39	18.655
32*	HO-C_5H_6-NH-	7.47	19.136
35*	MeOOC-C_9H_8-NH-	7.18	20.914
41*	Ph-CH(CH_2OH)NH-	7.41	19.679

chi0v = valence connectivity index of zero order

TABLE 6.3: Relationship between chi1v and activity of compounds of third set

Comp. no.	Substituents (X)	Inhibitory activity(A)	chi1v
Subgroup -A			
34	HOOC-CH(i-pr)NH-	6.79	13.886
40	C_6H_{11}-CH(Me)NH-	6.84	14.637
39	C_9H_9-NH-	6.89	15.192
32	HO-C_5H_6-NH-	7.47	15.209
Subgroup -B			
37	HO-C_6H_{10}-NH-	6.91	14.137
31	Ph CH_2NH-	6.94	14.226
41	Ph-CH(CH_2OH)NH-	7.41	15.175
Subgroup -C			
33	Ph CH_2-CH(CH_3OH)NH-	6.16	15.658
36	HO-C_9H_7(Me)NH-	6.67	15.976
35	MeOOC-C_9H_8-NH-	7.18	16.531
38*	HO-C_9H_8O-NH-	7.39	14.226

chi1v = valence connectivity index of first order

The biological activity and the reactivity indices, log

TABLE 6.4: Relationship between KierA1 and activity of compounds of third set

Comp. no.	Substituents (X)	Inhibitory activity(A)	KierA1
Subgroup-A			
33	Ph CH_2-CH(CH_3OH)NH-	6.16	26.829
36	HO-C_9H_7(Me)NH-	6.67	26.189
34	HOOC-CH(i-pr)NH-	6.79	26.066
40	C_6H_{11}-CH(Me)NH-	6.84	25.659
39	C_9H_9-NH-	6.89	24.266
31	Ph CH_2NH-	6.94	23.895
Subgroup-B			
37	HO-C_6H_{10}-NH-	6.91	24.628
38	HO-C_9H_8O-NH-	7.39	24.667
41	Ph-CH(CH_2OH)NH-	7.41	26.611
35*	MeOOC-C_9H_8-NH-	7.18	26.887
32*	HO-C_5H_6-NH-	7.47	24.266

KierA1 = kappa alfa first order

TABLE 6.5: Relationship between MR and activity of compounds of third set

Comp. no.	Substituents (X)	Inhibitory activity(A)	MR
Subgroup-A			
37	HO-C_6H_{10}-NH-	6.91	114.655
31	Ph CH_2NH-	6.94	116.893
38	HO-C_9H_8O-NH-	7.39	118.025
41	Ph-CH(CH_2OH)NH-	7.41	123.988
32	HO-C_5H_6-NH-	7.47	124.473
Subgroup-B			
34	HOOC-CH(i-pr)NH-	6.79	111.854
40	C_6H_{11}-CH(Me)NH-	6.84	122.443
39	C_9H_9-NH-	6.89	124.627
35	MeOOC-C_9H_8-NH-	7.18	134.111
33*	Ph CH_2-CH(CH_3OH)NH-	6.16	127.61
36*	HO-C_9H_7(Me)NH-	6.67	130.473

MR = molar refractivity

TABLE 6.6: Relationship between MW and activity of compounds of third set

Comp. no.	Substituents (X)	Inhibitory activity(A)	MV
Subgroup-A			
34	HOOC-CH(i-pr)NH-	6.79	422.52
40	C_6H_{11}-CH(Me)NH-	6.84	432.602
39	C_9H_9-NH-	6.89	438.566
32	HO-C_5H_6-NH-	7.47	438.566
Subgroup-B			
33	Ph CH_2-CH(CH_3OH)NH-	6.16	456.581
36	HO-C_9H_7(Me)NH-	6.67	468.592
35	MeOOC-C_9H_8-NH-	7.18	480.603
Subgroup-C			
31	Ph CH_2NH-	6.94	412.528
38	HO-C_9H_8O-NH-	7.39	418.575
41	Ph-CH(CH_2OH)NH-	7.41	448.601
37*	HO-C_6H_{10}-NH-	6.91	420.548

MW = molecular weight

P; chi0v; chi1v; kierA1; MR and MW, of these derivatives are given in TABLES 5.1-5.6. A close look at the TABLE 5.1 indicates that successive addition of substitutents, -$CH_2CH=CH_2$; -CH_2Ph; -CH_2-4-NH_2Ph; -CH_2-4-CH_3Ph; -CH_2-4-CF_3Ph; -$CH_2CH=CHPh$(E) and -CH_2-4-CMe_3Ph increase hydrophobicity and also the inhibitory activity. But successive addition of substitutents, -CH_2-4-OHPh; -CH_2SPh; -CH_2-4-NO_2Ph; -$CH_2C_6F_5$ and -CH_2-4-IPh increase hydrophobicity but decrease the activity. It also indicates that there is a direct relationship between reactivity indices, KierA1; MR and MW, and inhibitory activity of this set of compounds. We have divided the compounds of TABLE 5.1 into two subgroups-A and B; and TABLES 5.2-5.6 into three subgroups-A, B and C. All the subgroups of TABLES 5.1, 5.2, 5.4 and 5.5 show direct relationships very clearly, except subgroup-B of TABLES 5.1-5.3 and subgroup-C of TABLE 5.2. Compounds which do not follow the sequential trend are indicated by*.

Third set

Third set contain eleven derivatives and their biological activity is also shown in term of inhibitory activity[15].

The inhibitory activity alongwith reactivity indices, log P; chi0v; chi1v; KierA1; MR and MW, are given in TABLES 6.1-6.6. Examination of TABLES 6.1 show that successive addition of substitutents, Ph CH_2-$CH(CH_3OH)NH$-; HO-$C_9H_7(Me)NH$-; HOOC-CH(i-pr)NH-; and HO-C_6H_{10}-NH- in subgroup-A while C_6H_{11}-CH(Me)NH-; C_9H_9-NH-; HO-C_9H_8O-NH- and Ph-$CH(CH_2OH)NH$- in subgroup-B decrease hydrophobicity but increase the activity. TABLE 6.2 shows inverse relationship. TABLES 6.3-6.6 show that biological activity has direct relationships with chi1v; KierA1; MR and MW. The inverse and direct relationship can be better represented by dividing the TABLES 6.1, 6.2, 6.4 and 6.5 into two sub groups: A and B, while the remaining TABLES 6.3 and 6.6 into three subgroups: A, B and C. Compounds which do not follow the sequential trend are indicated by*.

QSAR models

Multi linear regression analysis using the descriptors, Log P, chi0v, chi1v, KierA1 MR and MW, in different combinations have been tried but only the following equations have provided better results, which can be used as QSAR models. The cross validation coefficient and correlation coefficient of these models are presented in TABLE 8. The QSAR models have been divided in three sets:

TABLE 7: Predicted activity from PA1-PA7 as obtained from regression equations, RE1-RE7

Comp. no.	Inhibitory activity (A)	PA1	PA2	PA3	PA4	PA5	PA6	PA7
1	5.82	6.505	6.955	7.061	6.993	6.377	6.344	6.364
2	6.9	7.352	7.961	8.04	8.002	7.774	7.746	7.77
3	6.29	7.009	7.29	7.324	7.277	7.028	6.993	6.99
4	6.48	6.718	7.135	7.204	7.145	6.676	6.64	6.647
5	6.59	6.974	7.314	7.289	7.267	6.995	6.97	6.939
6	7.46	7.023	7.533	7.387	7.409	7.159	7.143	7.053
7	8.22	7.12	8.041	7.975	7.996	7.586	7.577	7.526
8	7.89	7.224	7.705	7.523	7.554	7.445	7.428	7.325
9	8.52	7.447	8.157	8.073	8.087	7.917	7.899	7.844
10	7.54	7.847	8.17	8.136	8.215	8.268	8.307	8.306
11	8.3	7.623	7.999	7.999	8.101	8.141	8.191	8.21
12	7.72	7.343	6.831	6.93	7.227	7.257	7.469	7.591
13	8.52	6.823	9.895	10.08	10.056	8.23	8.205	8.224
14	6.98	6.558	7.98	8.065	8.004	7.128	7.083	7.08
15	7.72	6.571	8.755	9.032	9.159	7.611	7.711	7.829
16	9.6	8.881	8.657	8.699	8.688	8.98	8.964	8.993
17	8.11	8.636	8.889	8.79	8.843	8.922	8.915	8.867
18	9.72	9.127	8.824	8.831	8.831	9.301	9.284	9.302
19	9.59	9.429	8.107	8.21	8.108	9.381	9.384	9.482
20	9.64	9.457	9.335	9.306	9.29	9.881	9.842	9.839
21	9.22	9.314	7.273	7.529	7.371	9.004	9.034	9.23
22	9.54	9.171	8.899	8.843	8.872	9.355	9.349	9.338
23	9.51	8.395	8.87	8.882	8.846	8.724	8.686	8.676
24	9.57	8.911	8.515	8.641	8.57	9.106	9.084	9.162
25	9.8	8.705	8.541	8.597	8.562	8.839	8.82	8.854
26	7.56	8.238	7.874	7.89	7.868	7.945	7.927	7.932
27	9.14	9.661	9.55	9.189	9.025	9.986	10.039	9.89
28	8.27	8.306	8.666	8.729	8.697	8.627	8.6	8.622
29	9.6	8.749	9.098	8.995	8.985	9.108	9.092	9.039
30	9.77	9.89	9.451	9.161	9.283	10.294	10.31	10.207
31	6.94	7.778	6.985	7.053	7.018	6.914	6.897	6.922
32	7.47	8.056	7.489	7.549	7.551	7.434	7.435	7.462
33	6.16	7.703	7.165	7.195	7.151	7.09	7.063	7.067
34	6.79	7.266	6.047	5.978	5.976	6.116	6.127	6.099
35	7.18	8.069	7.647	7.648	7.668	7.657	7.664	7.667
36	6.67	7.628	7.538	7.523	7.539	7.201	7.205	7.185
37	6.91	7.182	6.603	6.606	6.601	6.282	6.285	6.275
38	7.39	7.854	6.941	6.878	6.913	6.964	6.972	6.945
39	6.89	7.966	7.51	7.565	7.566	7.369	7.367	7.388
40	6.84	8.11	7.107	6.963	7.035	7.283	7.302	7.244
41	7.41	7.623	6.936	6.876	6.892	6.886	6.887	6.856

The first set (RE1) has been developed using only log P. The correlation value of the model is below 0.60.

RE1=0.620278 Log P +5.53898

rCV^2=0.566415 r^2=0.59635

The second set (RE2-RE4) has been developed using the descriptors: chi1v, KierA1 MR and MW. The

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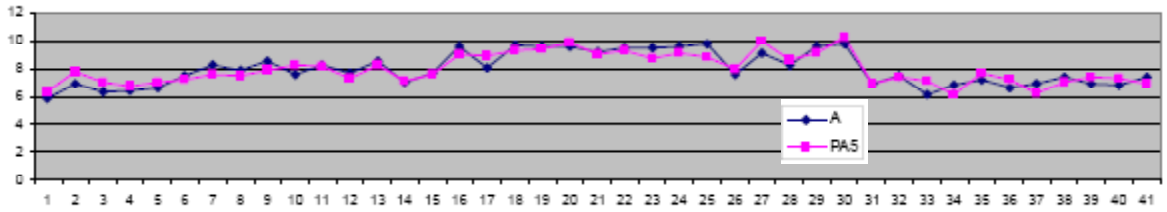

Figure 7: Graphic representation of relationship between fifth predicted activity (PA5) obtained from fifth regression equation (RE5) and observed activity (A) of the compounds

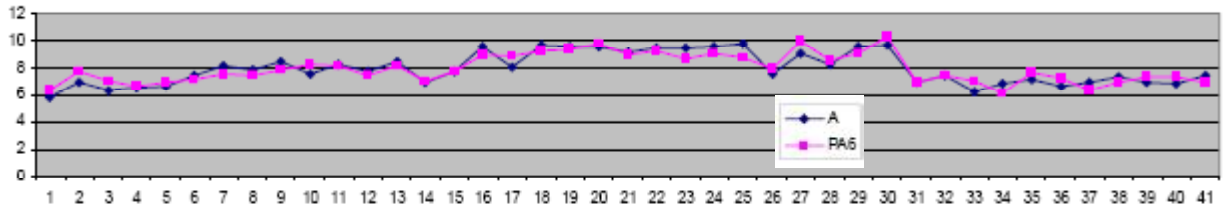

Figure 8 : Graphic representation of relationship between sixth predicted activity (PA6) obtained from sixth regression equation (RE6) and observed activity (A) of the compounds

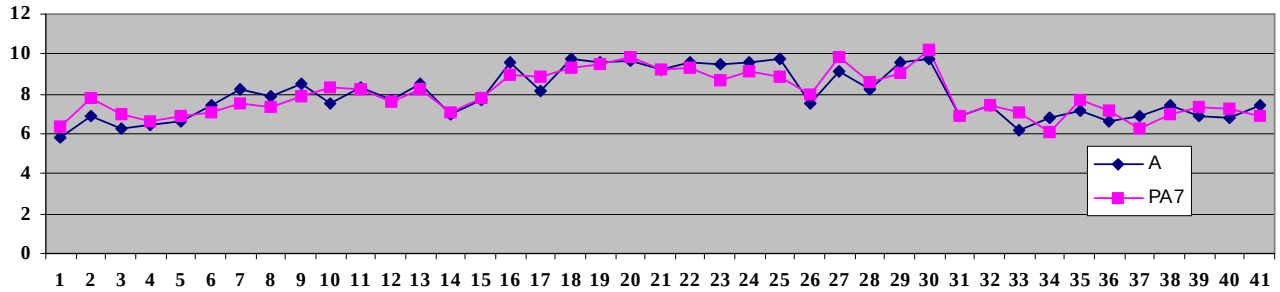

Figure 9: Graphic representation of relationship between seventh predicted activity (PA7) obtained from seventh regression (RE7) equation and observed activity (A) of the compounds

TABLE 8: The values of cross validation coefficient and correlation coefficient with combination of descriptors

Regression equation	rCV^2	r^2	Descriptor(s) used
RE1	0.566415	0.59635	Log P
RE2	0.48182	0.555834	chi1v, KierA1, MR
RE3	0.424793	0.543502	chi0v, KierA1, MR
RE4	0.500887	0.538817	KierA1, MW, MR
RE5	0.77206	0.802924	Log P, KierA1, MW, MR
RE6	0.770993	0.804	Log P, chi0v, KierA1, MR
RE7	0.760549	0.80768	Log P, chi1v, KierA1, MR

correlation values of these models are also below 0.60, hence can not considered as high class models.

RE2=-0.24875 chi1v -0.216955 KierA1+0.109446 MR +2.91411
rCV^2=0.48182 r^2=0.555834

RE3=-0.152724 chi0v -0.230804 KierA1+0.101157 MR+3.48108
rCV^2=0.424793 r^2=0.543502

RE4=-0.248168 KierA1-0.00320675 MW +0.0935459MR +3.33581
rCV^2=0.500887 r^2=0.538817

The third set (RE5-RE7) has been developed by using the combination of four reactivity indices e.g., log P; chi0v; chi1v; KherA1; MR and MW. The correlation values of these models are above 0.80 hence can be considered as high class models.

RE5=0.495205 Log P -0.0758793 KierA1-0.000262398MW +0.0438808 MR +1.91849
rCV^2=0.77206 r^2=0.802924

RE6=0.50345 Log P +0.0576518 chi0v-0.0895402 KierA1+0.0363927 MR +1.93135
rCV^2=0.770993 r^2=0.804

RE7=0.524553 Log P +0.130978 chi1v-0.0945474 KierA1+0.0278393 MR +2.17043
rCV^2=0.760549 r^2=0.80768

The predicted inhibitory activity of various derivatives as obtained from regression equations RE1-7 are presented in TABLE 7. A reference to these TABLES clearly indicates that predicted activities are close to observed activity. In order to adjudge their quality the values of cross validation coefficient and correlation coefficient, are collectively presented in TABLE 8

alongwith combination of descriptors. The values of correlation coefficients of QSAR models RE5, RE6 and RE7 are above 0.80, hence are considered as best models having reliable predictive power. The combinations of descriptors of these models are also shown in the TABLE 8. Graphs (Figures 7-9) between predicted activity and observed activity have been drawn for QSAR models RE5-RE7 to demonstrate the quality of prediction.

EXPERIMENTAL

The study materials of this paper are protease inhibitors and are presented in TABLES 1-3. TABLE 1 includes derivatives of urea isosteres[19] and TABLE 2, 3 includes derivatives of other isosteres[20]. The biological activity of these derivatives has been measured in term of inhibitory activity. For QSAR prediction, the 3D modeling and geometry optimization of all the derivatives of protease inhibitors have been done with the help of PCMODEL software using the semiemipical PM3 Hamiltonian[21]. The MOPAC calculations have been performed with Win MOPAC 7.21 software by applying key words: PM3, Charge = 0, Gnorm = 0.1, Bonds, Geo-OK, Vectors Density, and all the values required for the determination of the value of log P, valence connectivity index order 0, valence connectivity index order 1, shape index order 1, molar refractivity and molecular weight have been obtained from this software by solving the equations given in theory and result are reported in TABLES 4.1-6.6.

CONCLUSION

1. Out of the six descriptors that have used for studying the relationship with inhibitory activity of HIV-protease inhibitors, the log P is the best. In other words the hydrophobicity provides better relationship as compared with topological or steric indices.
2. Log P also is the essential descriptor of all combinations providing good QSAR model.
3. The best QSAR model (RE7) is provided by the combination of four descriptors, which are log P, chi1v, KherA1 and MR. The correlation coefficient values of this model is 0.80768.
4. Addition of substituent which increases the hydrophobicity also increases the inhibitory activity. Such substituents are Me, Et, i-Pr, t-Bu, 4-Py, $CHMe_2$ and CH_2CHMe_2. While substituents which decrease the hydrophobicity but increase the inhibitory activity are $PhCH_2$-$CH(CH_3OH)NH$-, HO-$C_9H_7(Me)NH$-, HOOC-CH(i-pr)NH- and HO-C_6H_{10}-NH-.

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