December 2008 Volume 4 Issue (6-8)

Organic CHEMISTRY

An Indian Journal

Trade Science Inc.

Full Paper

OCAIJ, 4(6-8), 2008 [391-400]

Study of forces governing the drug-receptor interaction of tetrahydroimidazodiazepinones (HIV-1-NNRTIs): A theoretical formalism

V.K.Sahu[1]*, A.K.R.Khan[2], R.K.Singh[2], P.P.Singh[1]

[1]Department of Chemistry, Bareilly College, Bareilly, U. P., (INDIA)

[2]Department of Chemistry, Maharani Lal Kunwari Post Graduate College, Balrampur, U.P., (INDIA)

E-mail: sahuvk2007@rediffmail.com

Received: 27th September, 2008 ; Accepted: 2nd September, 2008

ABSTRACT

To study various forces governing the drug-receptor interaction of a series of Tetrahydroimidazodiazepinones with their receptor, we have evaluated Log P and SASA for measurement of hydrophobic interaction; energy of protonation (ΔTE) for measurement of most favorable hydrogen bond acceptor site; bond length and bond strain for measurement of strength of hydrogen bond formed between drug and receptor; atomic charges, ionization potential (IP), electronegativity (χ), acidic ($E^{\#}n$) and basic atomic softness ($E^{\#}m$) and their difference ($\Delta E^{\#}nm$) for measurement of electrostatic interaction. The molecular modeling and geometry optimization of the compounds and receptor's aminoacids (Val, Met and Tyr) have been done by MOPAC-2002 associated with CaChe software. Softness Calculator has been used to evaluate effective atomic softness ($E^{\ddagger}n$ and $E^{\#}m$). The study have shown that hydrophobic interaction is predominant and made major contribution, while hydrogen bonding and polar interactions help in proper orientation of the compound (or its functional groups) to make maximam interaction. The overall strengths of these bonds determine the degree of affinity between the drug and the receptor.

KEYWORDS

Tetrahydroimidazodiazepinones;
NNRTIs binding pocket;
Hydrophobicity;
Hydrogen bond;
Effective atomic softness.

1. INTRODUCTION

In this article, we have studied various forces governing the drug-receptor interaction of a series of TIBO derivatives[1] with their receptor (NNRTIs binding pocket)[2,3]. The amino acids constituting the NNRTIs-pocket are Val (Y187), Met (Y184), and Tyr (Y181 and Y188). Since, Val and Met are hydrophobic in nature[4], they must play a major role in hydrophobic interaction. To analyze hydrophobic interaction[5], we have evaluated Log P and SASA of the substituents of each derivative and their effect on the activity of the compounds[6,7]. The hydrophobic nature of the NNRTIs pocket provides relatively few possibilities for polar interaction and hydrogen bonding. Amino acid, Tyr having phenolic group as its side chain only responsible for hydrogen bonding[8]. To analyze hydrogen bonding, we have searched out hydrogen bond donor and acceptor sites[9]. Then, the strength of hydrogen bonds formed between the most favorable hydrogen acceptor and donor sites have been evaluated by bond length and bond strain. The hydrophobic nature of the NNRTIs pocket provides relatively few possibilities for polar interaction. To analyze polar or electrostatic interaction, we have evaluated atomic charges, ionization potential, electronegativity, acidic and basic atomic softness.

2. Theory

On the basis of the nature of receptor's amino acids (Val, Met and Tyr) and nature of compound, we have selected following parameters for drug-receptor interaction: Log P and SASA for measurement of hydrophobic interaction; energy of protonation for measurement of most favorable hydrogen bond acceptor site; bond length and bond strain for measurement of strength of hydrogen bond formed between drug and receptor; atomic charges, ionization potential, electronegativity, acidic and basic atomic softness for measurement of electrostatic interaction. The values of the above parameters have been evaluated by using the various equations given below:

The molecular lipophilic potential (MLP)[10] was the first method designed to calculate the hydrophobic profile of a molecule in thre dimensions. The development of the MLP was based on the finding that the partition coefficient (P) of a molecule, which represents its relative distribution over an octanol/water boundary, can be estimated from its chemical structure[6].

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

From the assumption that the log P is an additive property of the molecular fragments that make up a molecule, values for a wide variety of atom types and groups have been calculated.

$$\pi_R = \log P - \log P_H \quad (2)$$

where π_X is the hydrophobicity of substient-R, log P is the hydrophobicity of the whole compound and log P_H is the hydrophobicity of the compound when substituent-R is replaced by hydrogen atom.

$$\pi_{X'} = \log P_R - \log P_{RX'} \quad (3)$$

where $\pi_{X'}$ is the hydrophobicity of substient-X', log P_R is the hydrophobicity of the compound where substituent-R is replaced by hydrogen and log $P_{RX'}$ is the hydrophobicity of the compound when substituent-R and X', both are replaced by hydrogen atoms.

One way to provide a simple account of surface properties is to compute the solvent-accessible surface area (SASA)[7]. SASA was first described by Lee and Richards in 1971 is sometimes called Lee-Richard molecular surface. SASA is typically calculated using the rolling ball algorithm developed by Shrake and Ruplet in 1973. This approach provides a useful tool to gain insight into the over all extent of a hydrophobic region on a molecule or in the binding site of a protein but lacks any real account of the particular atom types that make up the binding site or their positions relative to one another. In addition, it provides no means of assessing the shape of the binding since, it only calculates the relative accessibility of the contributing atoms.

$$^{R}SASA = SASA - {}^{H}SASA \quad (4)$$

where ^{R}SASA is the solvent accessible surface area of substient-R, SASA is the solvent accessible surface area of the whole compound and ^{H}SASA is the solvent accessible surface area of the compound where substituent-R is replaced by hydrogen atom.

$$^{X'}SASA = {}^{R}SASA - {}^{RX'}SASA \quad (5)$$

where $^{X'}$SASA is the solvent accessible surface area of substient-X′, ^{R}SASA is the solventaccessible surface area of the compound where substituent-R is replaced by hydrogen atom and $^{RX'}$SASA is the solventaccessible surface area of the compound where substituent-R and X', both are replaced by hydrogen atoms.

The total energy calculated by semiempirical methods has been shown to be a good descriptor in a number of different cases[11-14]. The total energy of a molecular system is the sum of the total electronic energy ($E_{ee.}$) and the energy of internuclear repulsion ($E_{nr.}$)

$$\text{Total energy (TE)} = E_{ee} + E_{nr.} \quad (6)$$

The energy of protonation defined as the difference between the total energies of the protonated and neutral forms of the molecule can be considered as a good measure of the strength of hydrogen bonds (the higher the energy, the stronger the bond) and can be used to determine the correct localization of the most favorable hydrogen bond acceptor site[9].

$$\Delta TE = TE - TE' \quad (7)$$

where ΔTE is the energy of protonation, TE is the total energy of neutral compound and TE' is the energy of protonated compound at a particular hydrogen acceptor site.

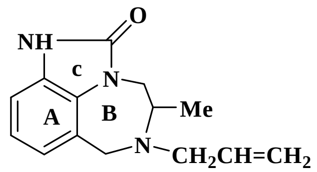
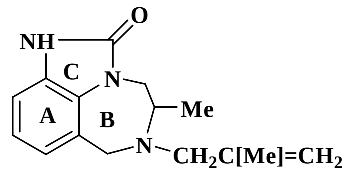
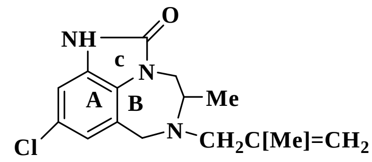
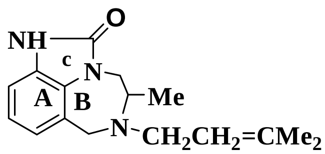
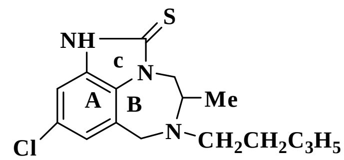
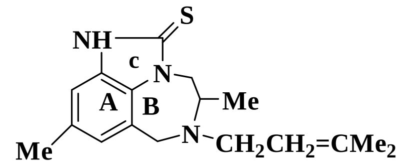
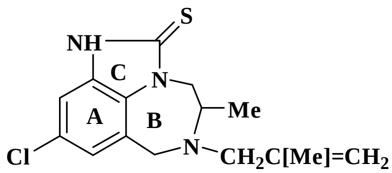
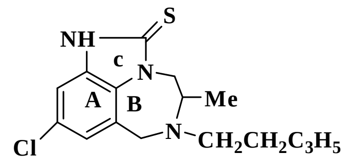
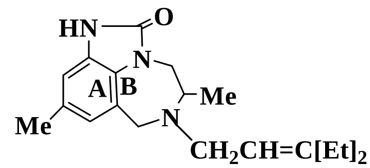
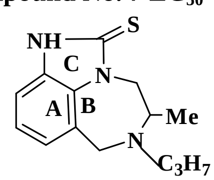
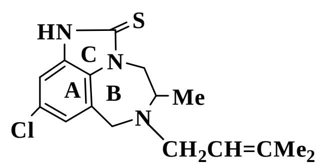
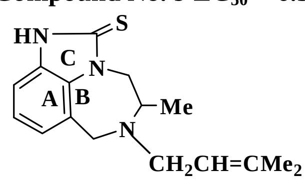
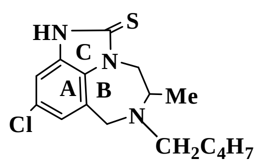
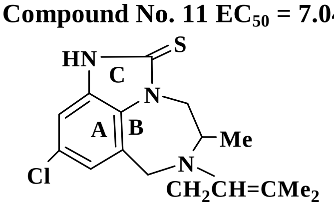
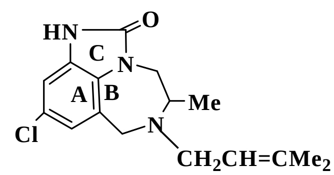
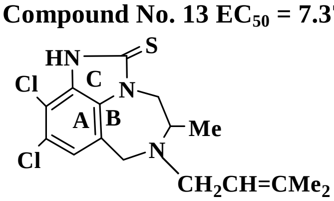
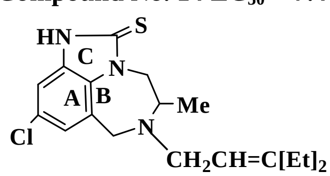
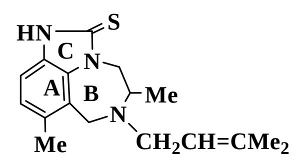
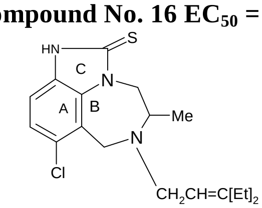
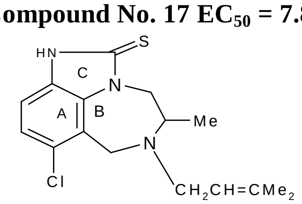
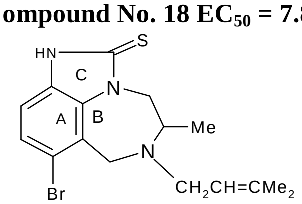
The softness of an atom in a molecule was described by Klopman[15] and modified by Singh et al.[16]. The Klopman equation is given by

$$E_n^{\#} = IP_n - b^2 (IP_n - EA_n) - [\chi_s (C_s^n)^2 / R_s] (1 - 1/\in)[q_s + 2b^2 \chi_s (C_s^n)^2] \quad (8)$$

$$E_m^{\#} = IP_m - a^2 - (IP_m - EA_m) [\chi_r (C_r^m)^2 / R_r] (1 - 1/\in)[q_r + 2b^2 \chi_r (C_r^m)^2] \quad (9)$$

where $E_n^{\#}$ is the softness of Lewis acid, $E_m^{\ddagger}$ is the softness of a Lewis base, IP is the ionization potential of atom, EA is the

TABLE 1: TIBO derivatives with their biological activity in terms of EC_{50}

 **Compound No. 1 EC_{50} = 4.23**	 **Compound No. 2 EC_{50} = 4.85**	 **Compound No. 3 EC_{50} = 5.33**
 **Compound No. 4 EC_{50} = 5.38**	 **Compound No. 5 EC_{50} = 5.66**	 **Compound No. 6 EC_{50} = 6.10**
 **Compound No. 7 EC_{50} = 6.35**	 **Compound No. 8 EC_{50} = 6.48**	 **Compound No. 9 EC_{50} = 6.51**
 **Compound No. 10 EC_{50} = 6.62**	 **Compound No. 11 EC_{50} = 7.04**	 **Compound No. 12 EC_{50} = 7.36**
 **Compound No. 13 EC_{50} = 7.37**	 **Compound No. 14 EC_{50} = 7.48**	 **Compound No. 15 EC_{50} = 7.60**
 **Compound No. 16 EC_{50} = 7.60**	 **Compound No. 17 EC_{50} = 7.82**	 **Compound No. 18 EC_{50} = 7.85**
 **Compound No. 19 EC_{50} = 8.29**	 **Compound No. 20 EC_{50} = 8.34**	 **Compound No. 21 EC_{50} = 8.52**

electron affinity of atom, $\in$ is the dielectric constant of the medium in which reaction is carried out. R, q are the radius and charge of atom s and r, C is the electron density, χ is q- (q-1)$\sqrt{k}$ and k = 0.75 and a, b is the variational parameter defined as $a^2 + b^2 = 1$.

It is well established that the stability of the compound formed between nucleophile and electrophile depends upon the value of difference between softness values of $E^{\#}m$ of nucleophile, and softness values of $E^{\ddagger}n$ of electrophile, $\Delta E^{\#}nm$ represent the difference. The higher is the $\Delta E^{\#}nm$ greater is the stability of the compound[17-21].

$$\Delta E^{\#}nm = | E^{\#}n - E^{\#}m | \qquad (10)$$

The method for the calculation of ionization potential of an atom in a molecule (IP) has been described by

Dewar and Morita[22] by the following equation.

$$IP = a+bq+cq^2 \quad (11)$$

where q is the charge of an atom in a molecule and C is the electron density of an atom in a molecule.

The method for calculation of the electron affinity of an atom in a molecule (EA) is given as[23]

$$EA = -(\varepsilon HOMO + \varepsilon LUMO) - (IP) \quad (12)$$

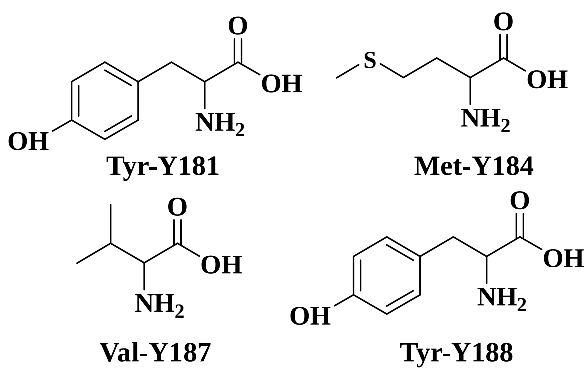
where HOMO and LUMO are the highest occupied and lowest unoccupied molecular orbital, respectively.

3. MATERIAL AND METHODS

Twenty one Tetrahydroimidazodiazepinone derivatives, that have been taken from literature, used as study material and are listed in TABLE 1 alongwith their observed biological activity in terms of EC_{50} (the concentration of compound leading to 50% effect and expressed in mol/l or mol/g). The logarithms of the inverse of EC_{50} have been used as biological end point (log1/C) in the study. For drug-receptor interaction, the molecular modeling and geometry optimization of all the derivatives have been carried out with CAChe Pro software by applying semiemperical method usimg MOPAC 2002. The parameters used for drug-receptor interaction: log P, solvent accessible surface area, energy of protonation, bond length, bond order, bond strain, atomic charges and atomic softness have also been evaluated by solving the various equations given in the theory same software. Log P is calculated using the atom-typing scheme of Ghose and Crippen[24]. The solvent accessible surface area (SASA) is calculated at an optimized geometry in water. The water geometry is from optimization first using Augmented MM2, then using MOPAC with PM3 parameters and the Conductor like Screeing Model (COSMO)[25]. The total energy is determined by a ZINDO calculation using INDO/1 parameters, at a geometry determined by optimization first with Augmented MM2 and then with MOPAC using PM3 parameters[26]. The partial charge calculated for an atom from quantum mechanics. Atom partial charges are determined by first optimizing the molecular geometry using Augmented MM2, followed by MOPAC with AM1 parameters. Values for bond property are ones that existed in the chemical sample when the extraction was evaluated. The fractional bond order (the distance between two bonded atoms) calculated from quantum mechanics. Bond orders are determined after geometry optimization using Augmented MM3 followed by MOPAC with PM3 parameters. The amount of steric (molecular mechanics) energy required to change the bond to its current length. Bond strain energies are determined after optimization using Augmented MM2. The atomic softness of every atom of all the derivatives has been done by Softness Calculator (It is a program in basic language created by us used for the calculation of hardness, softness, electronegativity, chemical potential, $E_n^{\#}$ and $E_m^{\#}$ with the help of above equations) by semiemperical methods. The reaction medium has been consider fresh water hence dielectric constant ($\in$) has been taken for fresh water 81[27].

4. RESULT AND DISCUSSION

The binding of the drug (compound) to the receptor will initially depend upon the types of chemical bonds (covalent bond, ionic bond, hydrogen bond and hydrophobic interactions) that can be established between the drug and its receptor. The overall strengths of these bonds will vary and will determine the degree of affinity between the drug and the receptor. The affinity of the compound for the receptor is dependent upon its proper three-dimensional characteristics such as: its size; stereochemical orientation of its functional groups; and its physical and electrochemical properties. In this paper we have chosen twenty-one tetrahydroimidazodiaze pinone (TIBO) derivatives for drug-receptor interaction. TIBO belongs to non-nucleoside group of reversetranscriptase inhibitors (NNRTIs). The NNRTIs interect non-competitively with an allosteric site of the reverse transcriptase enzyme and thus do not directly impair the function of the substrate binding site[28]. In fact, NNRTIs have a comparatively higher binding affinity for the enzyme-substrate complex than for the free enzyme itself. Their interaction with the enzyme leads to a conformational change in the enzyme, resulting in a decrease in the affinity of the active site for the substrate. However, NNRTIs are active against the RT of only HIV-1 and not of HIV-2 or any other retrovirus. This specificity of NNRTIs for the HIV-1-RT is due to presence in HIV-1-RT, and not in other RTs or DNA polymerases, of a flexible highly hydrophobic pocket in which a non-substrate analogue can fit snugly[29-31]. The hydrophobic pocket in HIV-1-RT is formed by the hydrophobic residues (Y181, Y184, Y187 and Y188) of the Y181-Y188 region[2]. The hydrophobic nature of the NNRTIs pocket provides relatively few possibilities for polar interaction and hydrogen bonding.



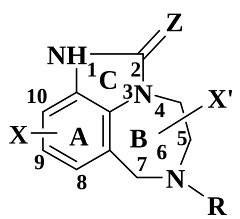


Figure 1

TABLE 2: Calculation of Log P of the substituents of TIBO derivatives

Log P at R-Substituent				Log P at X`-Substituent			
S.no.	log P	log P_H	π_R	S.no.	log P_R	log $P_{RX'}$	$\pi_{X'}$
1	1.265	0.163	1.102	1	0.163	-0.250	-0.087
2	1.419	0.163	1.256	2	0.163	-0.250	-0.087
3	1.937	0.681	1.256	3	0.681	0.268	0.413
4	1.770	0.163	1.607	4	0.163	-0.250	-0.087
5	3.432	2.361	1.071	5	2.361	1.948	0.413
6	2.237	0.631	1.606	6	0.631	0.217	0.414
7	3.616	2.361	1.255	7	2.361	1.948	0.413
8	4.326	2.361	1.965	8	2.361	1.948	0.413
9	3.030	0.631	2.399	9	0.631	0.217	0.414
10	3.015	1.843	1.172	10	1.843	1.430	0.413
11	3.967	2.361	1.606	11	2.361	1.430	0.931
12	3.449	1.843	1.606	12	1.843	1.430	0.413
13	3.828	2.361	1.467	13	2.361	1.948	0.413
14	3.967	2.361	1.606	14	2.361	1.948	0.413
15	2.288	0.681	1.607	15	0.681	0.268	0.413
16	4.485	2.879	1.606	16	2.879	2.466	0.413
17	4.760	2.361	2.399	17	2.361	1.948	0.413
18	3.917	2.310	1.607	18	2.310	1.897	0.413
19	4.760	2.361	2.399	19	2.361	1.948	0.413
20	3.967	2.361	1.606	20	2.361	1.948	0.413
21	4.241	2.635	1.606	21	2.635	2.221	0.413

On the basis of the nature of receptor's amino acids (Val; Met and Tyr), we have selected following parameters for drug-receptor interaction: Log P and SASA for measurement of hydrophobic interaction; energy of protonation for measurement of most favorable hydrogen bond acceptor site; bond length, bond order and bond strain for measurement of strength of hydrogen bond formed between drug and receptor; atomic charges, ionization potential, electronegativity, acidic and basic atomic softness for measurement of electrostatic interaction. The skeleton structure (Figure 1) of TIBO is based on following parent skeleton, which have 10 sites.

TABLE 3: Calculation of solvent accessible surface area (SASA) of the substituents of TIBO derivatives

SASA at R-Substituent				SASA at X`-Substituent			
S.no.	SASA	^{H}SASA	^{R}SASA	S.no.	^{R}SASA	^{RX}SASA	^{X}SASA
1	113.731	95.558	18.173	1	95.558	90.6170	4.941
2	118.740	95.698	23.042	2	95.698	90.7170	4.981
3	130.086	107.004	23.082	3	107.004	101.933	5.071
4	126.198	95.710	30.488	4	95.710	90.6210	5.089
5	137.395	115.401	21.994	5	115.401	110.291	5.110
6	133.326	102.689	30.637	6	102.689	97.6330	5.056
7	136.124	115.160	20.964	7	115.160	110.310	4.850
8	149.633	115.040	34.593	8	115.040	110.097	4.943
9	145.969	103.162	42.807	9	103.162	98.2980	4.864
10	123.043	103.530	19.513	10	103.530	98.8300	4.700
11	147.275	116.506	30.769	11	116.506	98.8300	17.67
12	136.434	105.244	31.190	12	105.244	98.9810	6.263
13	143.629	115.049	28.580	13	115.049	110.063	4.986
14	148.072	116.575	31.497	14	116.575	110.190	6.385
15	139.046	108.623	30.423	15	108.623	102.098	6.525
16	152.695	122.784	29.911	16	122.784	118.768	4.016
17	159.151	116.261	42.890	17	116.261	110.050	6.211
18	138.567	110.662	27.905	18	110.662	104.442	6.220
19	158.331	114.653	43.678	19	114.653	108.614	6.039
20	143.533	114.902	28.631	20	114.902	108.388	6.514
21	148.592	118.475	30.117	21	118.475	112.085	6.390

Tetrahydroimidazodiazepinone derivatives are included in TABLE 1, alongwith their observed biological activities in terms of EC_{50} values, as reported by Pauwels et al.[1]. The values of log P and SASA of the hydrophobic substituents of all the derivatives have been calculated and are presented in TABLES 2 and 3, respectively while, TABLE 4 represents their relationships with observed activity (EC_{50}). To analyze hydrogen bond interaction, we have evaluated energy of protonation to identify the hydrogen bond acceptors and to measure the most favourable hydrogen bondings and are presented in TABLE 5. The bond properties of various hydrogen bonds (formed between nitrogen at

TABLE 4: Calculation of hydrophobic parameters of TIBO drivatives and their relationships with observed activity (EC_{50})

Relationship between Log P and EC_{50}			Relationship between SASA and EC_{50}		
S.no.	**Log P**	**EC_{50}**	**s.no.**	**S.no.**	**SASA**
Subgroup-A			Subgroup-A		
21	4.241	8.520	17	159.151	7.820
20	3.967	8.340	16	152.695	7.600
14	3.967	7.480	14	148.072	7.480
13	3.828	7.370	13	143.629	7.370
12	3.449	7.360	12	136.434	7.360
9	3.030	6.510	7	136.124	6.350
6	2.237	6.100	6	133.326	6.100
4	1.770	5.380	3	130.086	5.330
2	1.419	4.850	2	118.740	4.850
Subgroup-B			1	113.731	4.230
19	4.760	8.290	Subgroup-B		
17	4.760	7.820	21	148.592	8.520
16	4.485	7.600	20	143.533	8.340
8	4.326	6.480	18	138.567	7.850
7	3.616	6.350	5	137.395	5.660
10	3.015	6.620	4	126.198	5.380
Subgroup-C			Subgroup-C		
18	3.917	7.850	19	158.331	8.290
5	3.432	5.660	11	147.275	7.040
15	2.288	7.600	9	145.969	6.510
3	1.937	5.330	10	123.043	6.620
1	1.265	4.230	8*	149.633	6.480
11*	3.967	7.040	15*	139.046	7.600

*** indicates compounds do not follow sequential trend**

TABLE 5: Calculation of energy of protonation of hydrogen bond acceptors on TIBO derivatives

Energy of protonation at site-3				Energy of protonation at site-6			
S.no.	**TE**	**TE**	**ΔTE**	**S.no.**	**TE**	**TE**	**ΔTE**
1	-129.310	-129.346	0.036	1	-129.346	-128.638	0.708
2	-136.500	-136.536	0.036	2	-136.536	-135.826	0.710
3	-148.271	-148.303	0.032	3	-148.303	-147.595	0.708
4	-143.684	-143.721	0.037	4	-143.721	-143.011	0.710
5	-145.688	-145.731	0.043	5	-145.731	-145.032	0.699
6	-150.877	-150.910	0.033	6	-150.910	-150.198	0.712
7	-145.431	-145.459	0.028	7	-145.459	-144.779	0.680
8	-154.399	-154.445	0.046	8	-154.445	-153.756	0.689
9	-165.188	-165.226	0.038	9	-165.226	-164.513	0.713
10	-128.309	-128.358	0.049	10	-128.358	-127.666	0.692
11	-152.792	-153.010	0.218	11	-153.010	-151.971	1.039
12	-140.838	-140.898	0.060	12	-140.898	-140.203	0.695
13	-152.915	-152.962	0.047	13	-152.962	-152.269	0.693
14	-152.611	-152.659	0.048	14	-152.659	-151.971	0.688
15	-155.455	-155.492	0.037	15	-155.492	-154.783	0.709
16	-164.372	-164.433	0.061	16	-164.433	-163.732	0.701
17	-166.918	-166.975	0.057	17	-166.975	-166.280	0.695
18	-148.023	-148.076	0.053	18	-148.076	-147.379	0.697
19	-166.901	-166.972	0.071	19	-166.972	-166.283	0.689
20	-152.600	-152.661	0.061	20	-152.661	-151.960	0.701
21	-150.718	-150.773	0.055	21	-150.773	-150.092	0.681

site-6 and hydrogen of side chain of tyrosine residue at Y188; between nitrogen at Site-3 and hydrogen of side chain of tyrosine residue at Y188; and between hydro-

TABLE 6 : Calculation of bond properties of hydrogen bond (H-Bond) formed between nitrogen at site-6 and hydrogen of side chain of tyrosine (Y188)

S.no.	H-Bond	$N^{\delta-}$	$H^{\delta+}$	Bond length	Bond strain
1	$^{\delta-}$H----O$^{\delta+}$	-0.292	0.240	2.514	0.007
2	$^{\delta-}$H----O$^{\delta+}$	-0.318	0.234	2.532	0.234
3	$^{\delta-}$H----O$^{\delta+}$	-0.326	0.235	2.537	0.011
4	$^{\delta-}$H----O$^{\delta+}$	-0.275	0.240	2.700	0.021
5	$^{\delta-}$H----O$^{\delta+}$	-0.284	0.237	4.097	0.035
6	$^{\delta-}$H----O$^{\delta+}$	-0.274	0.230	4.893	0.049
7	$^{\delta-}$H----O$^{\delta+}$	-0.259	0.233	2.936	0.075
8	$^{\delta-}$H----O$^{\delta+}$	-0.288	0.235	3.553	0.154
9	$^{\delta-}$H----O$^{\delta+}$	-0.295	0.241	2.539	0.019
10	$^{\delta-}$H----O$^{\delta+}$	-0.284	0.227	4.262	0.235
11	$^{\delta-}$H----O$^{\delta+}$	-0.280	0.238	2.653	0.018
12	$^{\delta-}$H----O$^{\delta+}$	-0.275	0.236	2.512	0.105
13	$^{\delta-}$H----O$^{\delta+}$	-0.277	0.236	4.218	0.051
14	$^{\delta-}$H----O$^{\delta+}$	-0.274	0.239	2.628	0.031
15	$^{\delta-}$H----O$^{\delta+}$	-0.278	0.235	3.676	0.123
16	$^{\delta-}$H----O$^{\delta+}$	-0.295	0.235	4.551	0.001
17	$^{\delta-}$H----O$^{\delta+}$	-0.281	0.239	4.063	0.050
18	$^{\delta-}$H----O$^{\delta+}$	-0.282	0.239	3.976	0.011
19	$^{\delta-}$H----O$^{\delta+}$	-0.277	0.238	2.839	0.099
20	$^{\delta-}$H----O$^{\delta+}$	-0.277	0.235	3.653	0.062
21	$^{\delta-}$H----O$^{\delta+}$	-0.277	0.236	3.970	0.091

TABLE 7: Calculation of bond properties of hydrogen bond (H-Bond) formed between nitrogen at site-3 and hydrogen of side chain of tyrosine (Y188) at site-3

S. no.	H-Bond	$N^{\delta-}$	$H^{\delta+}$	Bond length	Bond strain
1	$^{\delta-}$H----O$^{\delta+}$	-0.223	0.249	3.742	9.026
2	$^{\delta-}$H----O$^{\delta+}$	-0.261	0.248	5.109	8.442
3	$^{\delta-}$H----O$^{\delta+}$	-0.227	0.245	4.534	7.807
4	$^{\delta-}$H----O$^{\delta+}$	-0.230	0.229	4.911	9.706
5	$^{\delta-}$H----O$^{\delta+}$	-0.178	0.219	4.258	9.877
6	$^{\delta-}$H----O$^{\delta+}$	-0.184	0.254	5.779	10.264
7	$^{\delta-}$H----O$^{\delta+}$	-0.192	0.234	4.372	9.813
8	$^{\delta-}$H----O$^{\delta+}$	-0.178	0.246	4.453	10.139
9	$^{\delta-}$H----O$^{\delta+}$	-0.216	0.246	3.745	8.733
10	$^{\delta-}$H----O$^{\delta+}$	-0.195	0.236	3.588	10.098
11	$^{\delta-}$H----O$^{\delta+}$	-0.190	0.246	4.457	9.649
12	$^{\delta-}$H----O$^{\delta+}$	-0.188	0.249	4.054	9.770
13	$^{\delta-}$H----O$^{\delta+}$	-0.192	0.234	6.434	9.690
14	$^{\delta-}$H----O$^{\delta+}$	-0.189	0.246	4.457	9.640
15	$^{\delta-}$H----O$^{\delta+}$	-0.225	0.225	4.528	10.734
16	$^{\delta-}$H----O$^{\delta+}$	-0.180	0.247	3.721	9.724
17	$^{\delta-}$H----O$^{\delta+}$	-0.197	0.233	3.675	9.826
18	$^{\delta-}$H----O$^{\delta+}$	-0.187	0.231	4.631	9.036
19	$^{\delta-}$H----O$^{\delta+}$	-0.186	0.243	4.485	9.776
20	$^{\delta-}$H----O$^{\delta+}$	-0.191	0.248	4.524	10.508
21	$^{\delta-}$H----O$^{\delta+}$	-0.196	0.235	3.789	10.122

TABLE 8: Calculation of bond properties of hydrogen bond (H-Bond) formed between hydrogen at site-1 and oxygen of side chain of tyrosine (Y181)

S. no.	H-Bond	H^{δ}	$O^{\delta-}$	Bond length	Bond strain
1	$^{\delta+}H----O^{\delta-}$	0.268	-0.266	3.634	0.021
2	$^{\delta+}H----O^{\delta-}$	0.282	-0.245	2.782	0.064
3	$^{\delta+}H----O^{\delta-}$	0.275	-0.275	2.604	0.000
4	$^{\delta+}H----O^{\delta-}$	0.273	-0.267	2.945	0.024
5	$^{\delta+}H----O^{\delta-}$	0.298	-0.300	4.493	0.059
6	$^{\delta+}H----O^{\delta-}$	0.297	-0.300	1.852	0.052
7	$^{\delta+}H----O^{\delta-}$	0.295	-0.270	3.323	0.026
8	$^{\delta+}H----O^{\delta-}$	0.301	-0.283	3.259	0.021
9	$^{\delta+}H----O^{\delta-}$	0.275	-0.284	5.832	0.024
10	$^{\delta+}H----O^{\delta-}$	0.296	-0.300	2.496	0.006
11	$^{\delta+}H----O^{\delta-}$	0.301	-0.283	1.834	0.085
12	$^{\delta+}H----O^{\delta-}$	0.288	-0.268	3.433	0.025
13	$^{\delta+}H----O^{\delta-}$	0.300	-0.302	3.224	0.038
14	$^{\delta+}H----O^{\delta-}$	0.298	-0.301	2.662	0.026
15	$^{\delta+}H----O^{\delta-}$	0.259	-0.249	4.289	0.043
16	$^{\delta+}H----O^{\delta-}$	0.306	-0.279	1.819	0.026
17	$^{\delta+}H----O^{\delta-}$	0.301	-0.283	1.835	0.011
18	$^{\delta+}H----O^{\delta-}$	0.298	-0.281	1.837	0.020
19	$^{\delta+}H----O^{\delta-}$	0.300	-0.282	3.153	0.030
20	$^{\delta+}H----O^{\delta-}$	0.299	-0.301	1.848	0.062
21	$^{\delta+}H----O^{\delta-}$	0.301	-0.283	1.835	0.004

gen at site-1 and oxygen of side chain of Tyrosine residue at Y181) have been evaluated and are presented in TABLES 6 to 8. For polar interaction, acidic atomic softness (*E‡n*) and basic atomic softness ($E^{\#}$m) of the reactive sites of each derivative and their difference (*?E‡nm*) has been evaluated and are presented in TABLE 9 and TABLE 10.

Hydrophobic interactions play a crucial role in ligand- protein binding[32]. Most ligand binding sites contain at least one hydrophobic (nonpolar) region, with many demonstrating a clear preference for nonpolar ligands. In this case, out of four receptor's amino acids the two are hydrophobic (Met-Y184 and Val-Y187) in nature. In these, the valine (Val-Y187) amino acid is the second top most hydrophobic amino acid (first one is isoleucine) and is responsible for hydrophobic interaction with R-substituents of the compounds. While methionine (Met-Y184) is also hydrophobic in nature and its side chain has CH_3-S- fragment at the end, which is responsible hydrophobic interaction but with X'-substituents (CH_3-group) of the compounds. The substituent's hydrophobicity of all the derivatives have been calculated and are presented TABLE 2. A reference to this table indicates that $CH_2CH=C[Et]_2$ as R-substituents have highest value of log P (compound no-9, 17 and 19 having log P = 2.399); $CH_2CH=C[Me]_2$ have a median values (compound no-6, 11, 12, 14, 16, 20, and 21with log P = 1.606) and $CH_2CH_2C_3H_5$ have lowest value (compound no-5, log P = 1.071) vale of log P. While CH_3-group as X'-substituents has log P value 0.413. When both hydrophobic substituents-R and X' have been removed, there is great loss in the hydrophobicity of the compounds as clear from the negative values of log P of compounds-**(1, 2 and 4)**. The negative value of log P is an indication of hydrophilicity and loss of hydrophobicity. Thus, there must be a relationship between the hydrophobicity (log P) and activity of the drugs. A close look of **TABLE** 4 indicates there is a direct relationship between the hydrophobicity (log P) and activity of the compounds and as log P decreases activity decreases.

TABLE 9: $\Delta E^{\#}_{nm}$ values derived from $E^{\#}_{n}$ of carbon atom (-CONH-) of amino acids and $E^{\#}_{m}$ of oxygen (-CO-) and sulphur (-CS-) atom of the compounds

No.	A	$E^{\#}_{n}$	Tyr $E^{\#}_{n}$= 36.03969	Glu $E^{\#}_{n}$= 36.00171	Asn $E^{\#}_{n}$= 36.08613
			$\Delta E^{\#}_{nm}$	$\Delta E^{\#}_{nm}$	$\Delta E^{\#}_{nm}$
1	O	-21.5674	57.607	57.569	57.654
2	O	-21.5165	57.556	57.518	57.603
3	O	-21.251	57.291	57.253	57.337
4	O	-21.6042	57.644	57.606	57.690
5	S	-8.87875	44.918	44.880	44.965
6	S	-9.02001	45.060	45.022	45.106
7	S	-9.09032	45.130	45.092	45.176
8	S	-8.64563	44.685	44.647	44.732
9	O	-21.7132	57.753	57.715	57.799
10	S	-8.93743	44.977	44.939	45.024
11	S	-8.64372	44.683	44.645	44.730
12	S	-8.87625	44.916	44.878	44.962
13	S	-8.6988	44.738	44.701	44.785
14	S	-8.64575	44.685	44.647	44.732
15	O	-21.3191	57.359	57.321	57.405
16	S	-8.4333	44.473	44.435	44.519
17	S	-8.66098	44.701	44.663	44.747
18	S	-9.40715	45.447	45.409	45.493
19	S	-8.69364	44.733	44.695	44.780
20	S	-9.15172	45.191	45.153	45.238
21	S	-9.07213	45.112	45.074	45.158

Solvent accessible surface area (SASA) also provides a useful tool to gain insight into the over all extent of a hydrophobic region on a molecule or in the binding

TABLE 10: $\Delta E^{\#}_{nm}$ values derived from $E^{\#}_{n}$ of carbon (-CO-) and sulphur (-CS-) of the compounds and $E^{\#}_{m}$ of oxygen atom of amino acids (-CONH-)

No.	A	$E^{\#}_{n}$	Tyr $E^{\#}_{m}$=-22.3384	Glu $E^{\#}_{m}$=-22.2171	Asn $E^{\#}_{m}$=-22.5734
			$\Delta E^{\#}_{nm}$	$\Delta E^{\#}_{nm}$	$\Delta E^{\#}_{nm}$
1	C	41.99085	64.329	64.208	64.564
2	C	41.99191	64.330	64.209	64.565
3	C	42.0364	64.375	64.254	64.610
4	C	41.99277	64.331	64.210	64.566
5	C	56.85379	79.192	79.071	79.427
6	C	56.85717	79.196	79.074	79.431
7	C	57.11108	79.449	79.328	79.684
8	C	56.83739	79.176	79.054	79.411
9	C	41.95711	64.296	64.174	64.531
10	C	56.86086	79.199	79.078	79.434
11	C	56.8359	79.174	79.053	79.409
12	C	56.77247	79.111	78.990	79.346
13	C	56.926	79.264	79.143	79.499
14	C	56.83545	79.174	79.053	79.409
15	C	41.99724	64.336	64.214	64.571
16	C	56.5651	78.904	78.782	79.138
17	C	56.8469	79.185	79.064	79.420
18	C	56.98361	79.322	79.201	79.557
19	C	56.91424	79.253	79.131	79.488
20	C	57.1369	79.475	79.354	79.710
21	C	41.99085	64.329	64.208	64.564

site of a protein but lacks any real account of the particular atom types that make up the binding site or their positions relative to one another. In addition, it provides no means of assessing the shape of the binding, since it only calculates the relative accessibility of the contributing atoms. The substituent's SASA of all the derivatives have been calculated and are presented TABLE 3. A reference to this table indicates that $CH_2CH=C[Et]_2$ as R-substituents have highest value of SASA (34.593 to 43.678); $CH_2CH=C[Me]_2$ have values (30.117 to 31.497) somewhat lower than values of $CH_2CH=C[Et]_2$. While $CH_2CH2=CH_2$ have lowest value (18.173) of SASA. CH_3-group as X'-substituents has SASA value lower than R-substituents. A close look of TABLE 4 also indicates that there is a direct relationship between the SASA and activity of the compounds and as SASA decreases activity decreases. For a large hydrophobic object, it becomes impossible to maintain a hydrogen-binding network in its vicinity resulting in the disruption of the structure of water and a stronger hydrophobic interaction. The Lum-Chandler Weeks theory of hydrophobicity can account for the transition that occurs from the hydrophobic hydration of small nonpolar solutes to the strong tendency for depletion of water near extended nonpolar surfaces of nanometer length scale such as those in proteins.[33,34] Consequently, the computer simulation evidence and recent theoretical developments reveal the need to capture the stronger hydrophobic attraction that would arise between a ligand and a protein with a large or concave nonpolar surface. The strength of the hydrophobic interaction is thus influenced not only by the polarity but also by the shape and extent of the exposed molecular surface.

Hydrogen bonding is most likely an essential requirement for many drug-receptor interactions. A single hydrogen bond is relatively weak and would not be expected to support a drug-receptor interaction alone, but when multiple hydrogen bonds are formed between drugs and receptors, as is typically the case, a significant amount of stability is conferred upon the drug-receptor interaction. The energy of protonation defined as the difference between the total energies of the protonated and neutral forms of the molecule can be considered as a good measure of the strength of hydrogen bonds (the higher the energy, the stronger the bond) and can be used to determine the correct localization of the most favorable hydrogen bond acceptor site[9]. The TIBO derivatives have three nitrogen atoms, out of which two (at site-3 and 6) may act as hydrogen bond acceptor and the remaining one (at site-1) as donor. For correct localization of the most favorable hydrogen bond acceptor site, we have calculated energy of protonation of site-3 and 6 and are presented in TABLE 5. A reference to this table indicates that site-6 is the most favorable hydrogen bond acceptor site as it has higher energy of protonation (ranging from 0.680 to1.039) than site-3 (ranging from 0.028 to 0.218). In the hydrophobic pocket of the HIV-1-RTase, tyrosine amino acid constitutes the residues Y181 and Y188. The phenolic (-OH) group of the side chain of this amino acid has been evaluated to acts as hydrogen donor and thus formed H-bond with N-atom of site-6 and or with site-3. The bond properties of the H-bonds formed have been evaluated and are presented into TABLES 6 and 7. A reference to these tables indicate the H-bond formed between N-atom at site-6 and H-atom of Y188 residue have comparatively short bond length and lesser bond strain (most favourable H-bond) than H-bond formed between N-atom at site-3. Another most favourable H-bond is formed between H-atom of hydrogen donor (-NH-) at site-1 and O-atom of the phenolic (-OH) group of the side chain of tyrosine amino acid at Y181. The bond properties of the bond as evaluated are presented into TABLE 8.

The hydrophobic pocket in HIV-1-RT is formed by the hydrophobic residues (Y181, Y184, Y187 and Y188) of the Y181-Y188 region. The hydrophobic nature of the NNRTIs pocket provides relatively few possibilities for polar interaction and hydrogen bonding. The remaining residues of the Y181-Y188 region are Asn-Y182, Tyr-Y183, Glu-Y185 and Glu-Y186, and constitute the dNTP substrate-binding site. All these amino acids residues of Y181-Y188 region held together with the help of peptide bonds (-CONH-). The carbonyl group of amino acids of dNTP substrate binding may involve in the polar interaction with the polar groups on the compounds (ligands). The polar representations of the carbonyl group indicate that the carbon atom will be somewhat positive and the oxygen atom somewhat negative. This suggests two possible modes of reaction for a carbonyl group. The electron deficient (electrophilic) carbon atom can react with nucleophile, and the electron rich (nucleophilic) oxygen atom can react with electrophiles. We normally classify the reactions as nucleophilic addition because bond formation to the carbonyl carbon atom by an electron rich reagent is the most significant change that occurs. It is well established that the stability of the compound formed between nucleophile and electrophile depends upon the value of difference between softness values of $E^{\#}m$ of nucleophile, and softness values of $E^{\ddagger}n$ of electrophile, $\Delta E^{\#}nm$ represent the difference. The higher is the $\Delta E^{\#}nm$ ($\Delta E^{\#}nm = |E^{\#}n - E^{\#}m|$) greater is the stability of the compound[17-21].

$\Delta E^{\#}nm$ values, when the compounds treated as nucleophile and receptor amino acids (Asn-Y182, Tyr-Y183, and Glu-Y186) as electrophile, have shown that interaction occur between the compound (O/S-atom at site-2) and Asn Y182 amino acid (C-atom of carbonyl group of -CONH-), as the interaction have higher value of ?? $\Delta E^{\#}$ nm than interaction between Tyr-Y183 and Glu-Y185; 186, TABLE 9. While in the other case, the compounds (C-atom of site-2) treated as electrophiles and receptor amino acids (O-atom of carbonyl group of -CONH-) as nucleophiles, interaction occurs between the compound (C-atom at site-2) and Asn Y182 amino acid (O-atom of carbonyl group of (-CONH-), as the interaction have higer value of $\Delta E^{\#}nm$ than interaction between Tyr-Y183 and Glu-Y186; 186, TABLE 10. A reference to TABLES 9 and 10 indicates that later case has higher values of $\Delta E^{\#}nm$ than former and thus the compounds formed between Asn-Y182 amino acid and Tetrahydroimidazodiazepinone have higher stability.

The study have shown that hydrophobic interaction is predominant and made major contribution, while hydrogen bonding and polar interactions help in proper orientation of the compound (or its functional groups) to make maximam interaction. The overall strengths of these bonds determine the degree of affinity between the drug and the receptor.

ACKNOWLEDGMENTS

We thank Dr. Suhail Ahmad Khan for [Department of Chemistry, M.K.(P. G.) College, Balrampur, U. P., INDIA] valuable suggestions.

REFERENCES

[1] R.Pauwels, K.Andries, Z.Debyser, M.J.Kukla, D. Schols, H.J.Breslin, R.Woestenborghs, J.Desmyter, P.A.Janssen; J.Antimicob.Agents Chemother., **38**, 2863 **(1994)**.

[2] De Clercq, E.Med.Res.Rev., **13**, 229 **(1993)**.

[3] Debnath, A.K.Current Pharmaceutical Design, **11**, 3091-3110 **(2005)**.

[4] H.R.Horton, L.A.Moran, R.S.Ochs, J.D.Rawn, K.Scrimgeour; 'Principles of Biochemistry', New Jersey: Prentice Hall, 2nd ed., 57-60 **(1996)**.

[5] M.D.Kelly, R.L.Mancera; J.Med.Chem., **48**, 1069-1078 **(2005)**.

[6] T.Fujita, J.Iwasa, C.J.Hansch; Am.Chwm.Soc., **86**, 5174-5180 **(1964)**.

[7] B.Lee, F.M.Richards; J.Mol.Biol., **55**, 379-400 **(1971)**.

[8] H.R.Horton, L.A.Moran, R.S.Ochs, J.D.Rawn, K.G.Scrimgeour; 'Principles of Biochemistry', New Jersey: Prentice Hall, 2nd ed., 36 and 152 **(1996)**.

[9] G.Trapani, A.Carotti, M.Franco, A.Latrofa, G.Genchi, G.Liso; Fur.J.Med.Chem., **35**, 584 **(1992)**.

[10] E.Audry, J.P.Dubost, J.C.Colleter, P.Dallet; Eur.J. Med.Chem., **21**, 71-72 **(1986)**.
[11] C.Gruber, V.Buss; Chemosphere, **19**, 1595 **(1989)**.
[12] N.Bodor, Z.Gabanyi, C.K.Wong; J.Am.Chem.Soc., **111**, 3783 **(1989)**.
[13] K.Osmialowski, J.Halkiewicz, A.Radecki, R.J. Kaliszan; Chromatogr.Sci., **346**, 53 **(1985)**.
[14] F.Saura-Calixto, M.A.Garcia-Raso; J.Chromatogr. Sci., **22**, 22 **(1984)**.
[15] G.J.Klopman; Am.Chem.Ssoc., **90**, 223-234 **(1968)**.
[16] P.P.Singh, S.K.Srivastava, A.K.Srivastava; J. Inorg.Nucl.Chem., **42**, 521-532 **(1980)**.
[17] P.P.Singh, F.A.Pasha, H.K.Srivastava; QSAR and Combi.Sci., **22**, 843 **(2003)**.
[18] P.P.Singh, F.A.Pasha, H.K.Srivastava; Indian J. Chem.B., **43B**, 983-991 **(2004)**.
[19] P.P.Singh, F.A.Pasha, H.K.Srivastava; Molecular Diversity, **9**, 215-220 **(2005)**.
[20] P.P.Singh; Coord.Chem.Rev., **32**, 33 **(1980)**.
[21] P.P.Singh, K.Atreya; Polyhedron, **1**, 711 **(1982)**.
[22] M.J.S.Dewar, T.F.Morita; J.Chem.Phys., **110**, 9807-9811 **(1999)**.
[23] **(a)** R.G.Pearson; J.Am.Chem.Soc., **110**, 2092-2097 **(1988)**.
(b) R.G.Pearson; Inorg.Chem., **27**, 734-470 **(1988)**.
[24] A.K.Ghose et al.; J.Comput.Chem., **9**, 80 **(1988)**.
[25] A.Klamt, G.Schuurmann; J.Chem.Soc.Perkin Trans., **2**, 799 **(1993)**.
[26] J.J.P.Stewart; J.Comp.Chem., **10**, 221-264 **(1989)**.
[27] D.J.Daniels; The Institute of Electrical Engineers, **320**, **(1996)**.
[28] I.W.Althaus, J.J.Chou, A.J.Gonzales, M.R.Deibel, K.C.Chou, F.J.Kezdy, D.L.Romero, R.C.Thomas, P.A.Aristoff, W.G.Tarpley, F.Reusser; F.Biochem. Pharmacol., **47**, 2017 **(1994)**.
[29] A.Jacobo-Molina, J.Ding, R.G.Nanni, A.D.Clark, (Jr.); X.Lu, C.Tantillo, R.L.Williams, G.Kamer, A.L. Ferris, P.Clark, A.Hizi, S.H.Hughes, E.Arnold; E.Proc.Natl.Aczd.Sci.U.S.A., **90**, 6320 **(1993)**.
[30] R.G.Nanni, J.Ding, M.A.Jacobo, S.H.Hughes, E. Arnold; Perspect.Drug Discovery Des., **1**, 129 **(1993)**.
[31] L.A.Kohlstaedt, J.Wang, J.M.Friedman, P.A.Rice, T.A.Steitz; Science, **256**, 1783 **(1992)**.
[32] A.Ajay, M.A.Murcko; J.Med.Chem., **38**, 4953-4967 **(1995)**.
[33] K.Lum, D.Chandler, J.D.Weeks; J.Phys.Chem.B, **103**, 4570-4577 **(1999)**.
[34] D.M.Huang, D.Chandler; Proc.Natl.Acad.Sci. U.S.A., **97**, 8324-8327 **(2000)**.