September 2009 *Volume 5 Issue 3*

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 5(3), 2009 [296-304]

PM3 based calculations of interaction energy between metalloproteinases and hydroxamate inhibitors

R.K.Singh, Surabhi Rai, P.P.Singh*

Chemistry Department, M.L.K. (P.G.) College- Balrampur (U.P.), (INDIA)

E-mail : dr_ppsingh@sify.com

Received: 25th June, 2009 ; Accepted: 5th July, 2009

ABSTRACT

Metalloproteinases (MMP) are zinc-containing enzymes; that mediate the break down of connective tissue. The therapeutic inhibitors are chelating agents such as hydroxamates (RNHOH). The interaction between enzyme and the inhibitor is two fold. The nitrogen of RNHOH chelates with zinc, whereas the R substituent has polar interaction with histidine part of the enzyme. The chelating ability of the RNHOH has been studied with the help of transfer of charge ΔN and and lowering of energy ΔE on interaction of RNHOH with Zn^{++}. The magnitude of interaction has been evaluated by equation $\Delta N = (\chi^o_A - \chi^o_B)/ 2(\eta_A + \eta_B)$ and $\Delta E = -(\chi^o_A - \chi^o_B)^2 / 4(\eta_A + \eta_B)$. Based on DFT principles the interaction energy E_{int} between Zn^{++} of MMP and nitrogen of RNHOH has also been calculated by using the values of softness, chemical potential and number of electrons. The results of ΔN, ΔE and E_{int} have been compared. The interaction between R of RNHOH and histidine of the enzymes has been studied by identifying the sites of hydrogen bonding between hydrogen of histidine and sulphonyl, ester and carbonyl oxygen of inhibitors and vice versa. The study provides new descriptors, ΔN, ΔE, E_{int} for application in biological system.

KEYWORDS

Metallloproteinases;
Hydroxamate inhibitors;
Interaction energy;
Charge transfer;
Energy lowering.

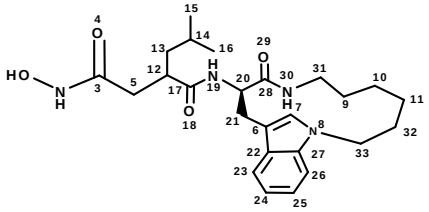
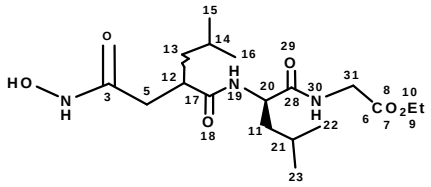
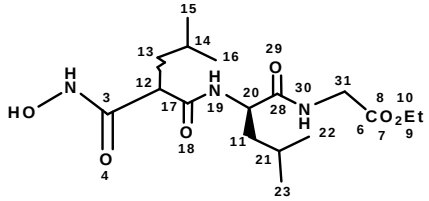
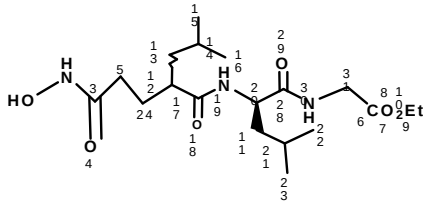
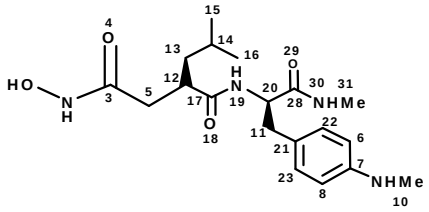
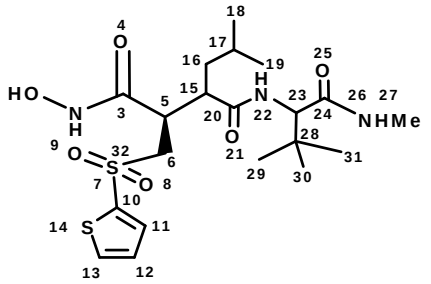
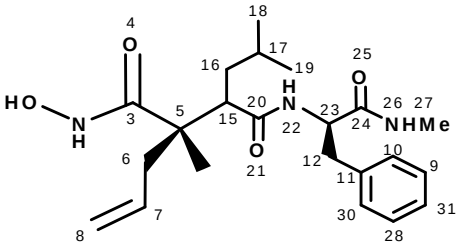
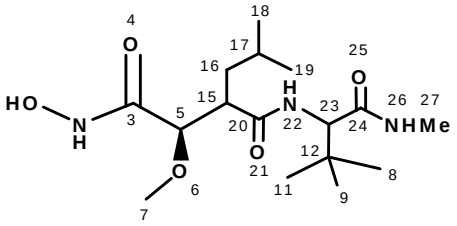
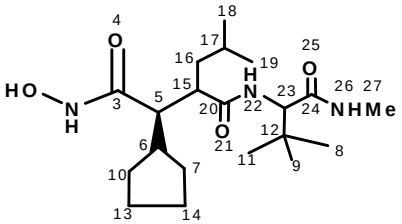
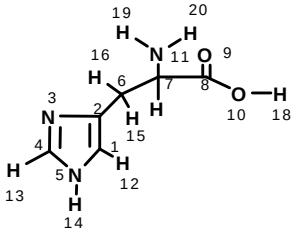
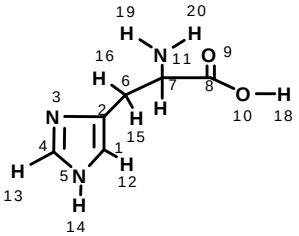
INTRODUCTION

The magnitude of interaction between a donor molecule (B) and acceptor (A) has been measured in terms of transfer of energy (ΔN) from B to A and lowering of energy (ΔE) on the formation of A-B[1]. The interaction has also been measured in terms of interaction energy (E_{int})[2]. The essential requirements for measurement are electronegativity, absolute hardness, of A and B for ΔE, and ΔN, where as for interaction energy chemical potential and number of electrons of A and B are required. The relevant equation of ΔE, ΔN and E_{int} are described under material and method. The applications of these energies have never been made in biological system, though donor-acceptor strength between inhibitor and receptor is well known in metalloproteinases[3,4] and carbonic anlydrase[5]. In this paper we have evaluated ΔN, ΔE and interaction energy (E_{int}) between the receptor zinc of metalloproteinases (MMP) and hydroxamate inhibitors (RNHOH) and have also identified site of hydrogen bonding between enzyme and inhibitors. On the basis of results of these energies the activity of inhibitors has been proposed.

MATERIAL AND METHOD

The study materials of this paper are ten derivatives of hydroxylamine (RNHOH), which have been used as synthetic inhibitors of MMP[6-8]. The geometry of these compounds has been optimized with the help of CAChe software by PM3 method. The optimized structures are shown in TABLE 1. The values of electronegativity, chemical potential (μ), absolute hardness (η), number of electrons (N) and Lambda (λ) have also been evaluated with the same software by solving the equations given below:

TABLE 1 : List of compounds and their structures

Comp.	Structure	Comp.	Structure
EC1		EC2	
EC3		EC4	
EC5		EC6	
EC7		EC8	
EC9		EC10	
Histidine			

Full Paper

Interaction energy

Interaction between a stable molecule A formed by the bonding of K atom with a total number of electrons N_A and a stable molecule B formed by the bonding of L atom with a total number of electrons N_B in terms of interaction energy is given by equation-1 according to density functional theory[2].

$$\Delta E_{int} = E[\rho_{AB}] - E[\rho_A] - E[\rho_B] \quad (1)$$

It has been shown that if the interaction energy is divided into two steps and one makes use of the properties of the hardness and softness functions, then the equation-1 can be written in the form:

$$\Delta E_{int} = \Delta E_v + \Delta E\mu \quad (2)$$

Where

$$\Delta E_v \approx -[(\mu_A + \mu_B)^2 / 2(S_A+S_B)] \times (S_A S_B) \quad (3)$$

And

$$\Delta E\mu \approx -\lambda / 2(S_A+S_B) \quad (4)$$

S = softness, μ = Chemical potential

Charge transfer (ΔN) and energy lowing (ΔE)

When Lewis acid (electrophile) reacts with Lewis base (nucleophile) or when there is metal ligand interaction, there is a shift of electrons from the Lewis base to Lewis acid, until the chemical potentials of both become equal[9]. The condition of equilibrium is that the chemical potential, μ_A and μ_B, become equal. This leads to shift in charge, ΔN, from less electronegative base (B) to more electronegative acid (A).

$$\Delta N = (\chi^o_A - \chi^o_B) / 2(\eta_A + \eta_B) \quad (5)$$

Electron transfer leads to an energy lowering given by equation 7.

$$\Delta E = -(\chi^o_A - \chi^o_B)^2 / 4(\eta_A + \eta_B) \quad (6)$$

Where χ = Electronegativity, η = Absolute hardness

In equations 5 and 6 the electronegativity difference derive the electron transfer, and the sum of hardness parameters inhibits it[10].

RESULT AND DISCUSSION

Matrix metalloproteinases (MMPs), also called matrixins are a family of structurally related zinc containing enzymes (Figure 1) that mediate the breakdown of connective tissues and are therefore targets for therapeutic inhibitors in many inflammatory, malignant and degenerative diseases[11-13]. In normal condition the enzyme and the substrate exist without causing any degradation of substrate because the naturally occurring inhibitors (specific-TIMP, nonspecific-α-macroglobulins) keep a check over the degrading character of the enzymes. An imbalance between MMPs and naturally occurring MMP- inhibitors may cause excess extracellular matrix destruction. When endogenous inhibitors cannot control the over expression of MMPs, synthetic inhibitors are required. The principal approach for the design of an effective inhibitor is substrate based design and a ZBG which has ability of chelating the active site Zn (II) present in the enzyme. Hydroxamic acid is one such example, (Figure 2) which has chelating property and its peptide derivatives have been recognized as successful inhibitors[14]. The Zn^{++} of the MMP acts as electrophile and the hydroxamates as nucleophiles.

The inhibitor- receptor interaction is basically a donor acceptor interaction; the peptide part provides hydrogen bonding and polar interaction. In the present case we have divided our discussion in two parts. The donor acceptor interaction between Zn^{++} and nitrogen of RNHOH and the interaction between histidine and the peptidic part (R) of RNHOH. The parent structure of MMP is given in Figure 1, and that of hydroxamate inhibitors in Figure 2.

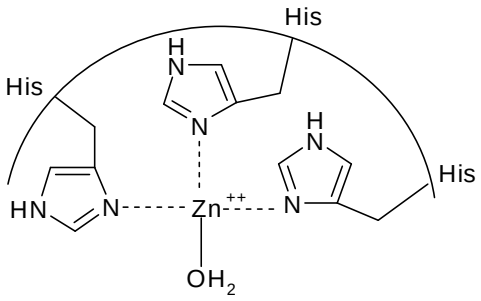


Figure 1

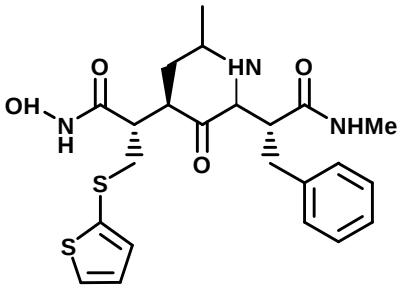


Figure 2

In a donor acceptor interaction the electronegativity, absolute hardness, chemical potential and number of electrons of donor and acceptor play an important role. The values of these parameters have been obtained with the help of CAChe software. With the help of these values equations-1, 5 and 6 have been solved for evaluating the magnitude of interaction between acceptor metalloproteinases (MMP) and hydroxamate inhibitors (RNHOH). The results of solution of equations, have provided the values of ΔN and ΔE which are included in TABLE 2 and of energy interaction (E_{int}) in TABLE 3. A reference to TABLE 2, indicate that there is a shift of charge from less electronegative hydroxamate inhibitors (B) to more electronegative Zn++ receptor (A). The ΔN values indicate that the magnitude of interaction is maximum with EC-2, and minimum with EC-3. The sequence is EC2 > EC1 > EC6 > EC7 > EC10 > EC8 > EC9 > EC5 > EC4 > EC3. The ΔE also shows the same order of magnitude of interaction, with only one change in case of EC-10. The results show that lower is the value of electronegativity of RNHOH, better will be the inhibitor.

TABLE 2 : ΔN and ΔE values in eV obtained by interaction of hydroxamates and Zn^{++}

Compound	χ_A	χ_B	η_B	η_A	ΔN	ΔE
EC1	-26.344	-8.683	-2.960	-4.027	-1.263847	11.160402
EC2	-26.344	-8.008	-2.527	-4.027	-1.398985	12.826247
EC3	-26.344	-9.168	-3.954	-4.027	-1.076056	9.241166
EC4	-26.344	-9.297	-3.278	-4.027	-1.166918	9.946514
EC5	-26.344	-9.133	-2.790	-4.027	-1.262488	10.864657
EC6	-26.344	-8.324	-2.688	-4.027	-1.341909	12.090938
EC7	-26.344	-8.536	-2.913	-4.027	-1.282997	11.423806
EC8	-26.344	-8.814	-3.729	-4.027	-1.130198	9.906467
EC9	-26.344	-9.061	-3.901	-4.027	-1.090098	9.420352
EC10	-26.344	-8.991	-3.928	-4.027	-1.090698	9.463438

A=Zn^{++}, B=Inhibitor (Hydroxamate), χ=Electronegativity, η=Absolute hardness, ΔN=Charge transfer, ΔE=Energy lowering

TABLE 3 : Interaction energy in eV for interaction energy of A and B

Comp.	μ_B	S_B	μ_A	S_A	N_B	N_A	λ	Eν	Eμ	E_{int}
EC1	8.683	0.338	26.344	0.248	160	0	25.600	-22.321	-21.837	-44.158
EC2	8.008	0.396	26.344	0.248	166	0	27.556	-25.652	-21.390	-47.043
EC3	9.168	0.253	26.344	0.248	142	0	20.164	-18.482	-20.114	-38.597
EC4	9.297	0.305	26.344	0.248	136	0	18.496	-19.893	-16.710	-36.603
EC5	9.133	0.358	26.344	0.248	148	0	21.904	-21.729	-18.048	-39.778
EC6	8.324	0.372	26.344	0.248	136	0	18.496	-24.182	-14.906	-39.088
EC7	8.536	0.343	26.344	0.248	162	0	26.244	-22.848	-22.180	-45.028
EC8	8.814	0.268	26.344	0.248	140	0	19.600	-19.813	-18.973	-38.786
EC9	9.061	0.256	26.344	0.248	126	0	15.876	-18.841	-15.728	-34.569
EC10	8.991	0.255	26.344	0.248	142	0	20.164	-18.927	-20.047	-38.974

A=Zn^{++}, B=Inhibitor (Hydroxamate), S=Softness, μ=Chemical potential, N=Number of electrons

The interaction energy (E_{int}) calculated for receptor- inhibitor interaction is presented in TABLE 3. A reference to this Table indicates that similar to ΔN and ΔE the best interaction is shown by compound EC-2. The magnitude of interaction measured by interaction energy is not exactly similar to the sequence shown by ΔN and ΔE, but in respect of trend it can also provide useful information.

HOMO energy of base and LUMO energy of acid also provide useful information about the magnitude of interaction between metal and ligand. When a reaction takes place between acid and base transfer of electron from HOMO of base to LUMO of acid takes place. Soft base has high energy of HOMO and soft acid has low energy of LUMO and their reaction with each other is fast[20]. The lower is the value of difference between the energy of HOMO and LUMO greater will be the stability[15-18].

In the present case LUMO energy of the receptor $Zn^{++}$and HOMO energy of the inhibitor and the difference between them has been evaluated and are presented in TABLE 4. The ΔLH(E) values suggest the following order for donor acceptor strength. 2>7>6>10>8>9>5>7>4>3. This order is almost similar to the order derived from ΔN and ΔE.

Full Paper

TABLE 4 : Energy HOMO and LUMO and ΔLH(E)

Compound	HOMO energy(eV) Of Hydroxamates	LUMO Energy(eV) of Zn^{++}	ΔLH(E)
EC1	-9.023	-22.317	13.294
EC2	-8.717	-22.317	13.6
EC3	-9.972	-22.317	12.345
EC4	-9.937	-22.317	12.38
EC5	-9.886	-22.317	12.431
EC6	-9.113	-22.317	13.204
EC7	-9.911	-22.317	12.406
EC8	-9.715	-22.317	12.602
EC9	-9.725	-22.317	12.592
EC10	-9.44	-22.317	12.877

The results of ΔN, ΔE, E_{int} and ΔLH(E) indicate that hydroxamate derivatives, which have low value of number of electrons, are better chelating agents. Aromatic rings in the substituents-R of RNHOH also provide better interaction.

Hydrogen bonding: The receptor Zn^{++} is attached to three-histidine molecules. Histidine is a polar amino acid[19]. The inhibitor hydroxamates are peptide derivatives of hydroxamic acid (RNHOH). The group(R) attached to NH_2OH has also number of polar sites. The interaction between polar sites of receptor histidine and the polar sites of RNHOH has also been examined in respect of their polar interaction in terms of hydrogen bonding. Hydrogen bonding is most likely an essential requirement for many drug-receptor interactions. A single hydrogen bond is relatively weak, hence multiple hydrogen bonding has been recognized as more favorable[20,21]. In earlier reviews it is pointed out that the hydroxamate nitrogen after protonation forms a hydrogen bond with a carbonyl oxygen of the enzyme backbone of neutrophil collagenase[22,23]. The site of hydrogen bonding has not been mentioned in earlier work. For the purpose of finding the possible sites that are involved in hydrogen bonding the values of partial charge on each atom of inhibitors (EC-1-EC-10) has been evaluated and are presented in TABLES 5-14. The possible atoms that involve in hydrogen bonding are oxygen and nitrogen hence partial charges on oxygen and nitrogen of R of RNHOH have been identified and are included in TABLE 15. The values indicate that all oxygen atoms have negative charge and nitrogen atoms have positive charge, hence oxygen atoms have been considered for possible hydrogen bonding.

TABLE 5 : Partial charge of atoms of the compound EC1

Atom	Partial Charge	Atom	Partial Charge
C3	0.255	O18	-0.351
O4	-0.081	N19	0.006
C5	-0.102	C20	-0.073
C6	-0.222	C21	-0.088
C7	-0.64	C22	-0.092
S8	0.416	C23	-0.093
C9	-0.18	C24	-0.086
C10	-0.143	C25	-0.105
C11	0.072	C26	-0.125
C12	-0.127	C27	-0.136
C13	-0.114	C28	0.223
C14	-0.077	O29	-0.353
C15	-0.12	N30	-0.051
C16	-0.114	C31	-0.08
C17	0.23	S32	0.616

TABLE 6 : Partial charge of atoms of the compound EC2

Atom	Partial Charge	Atom	Partial Charge
C3	0.367	N19	0.38
O4	-0.185	C20	-0.158
C5	-0.124	C21	0
C6	-0.227	C22	-0.071
C7	-0.167	C23	-0.08
N8	0.269	C24	-0.098
C9	-0.109	C25	-0.082
C10	-0.122	C26	-0.08
C11	-0.102	C27	-0.148
C12	-0.065	C28	0.206
C13	-0.109	O29	-0.375
C14	-0.07	N30	0.006
C15	-0.124	C31	-0.092
C16	-0.119	C32	-0.122
C17	0.081	C33	-0.093
O18	-0.206		

TABLE 7 : Partial charge of atoms of the compound EC3

Atom	Partial Charge	Atom	Partial Charge
C3	0.368	C16	-0.119
O4	-0.182	C17	0.095
C5	-0.124	O18	-0.205
C6	0.359	N19	0.373
O7	-0.404	C20	-0.144
O8	-0.245	C21	-0.078
C9	0.083	C22	-0.116
C10	-0.149	C23	-0.117
C11	-0.136	C28	0.223
C12	-0.065	O29	-0.36
C13	-0.108	N30	0.032
C14	-0.07	C31	-0.1
C15	-0.124	C31	-0.1

TABLE 8 : Partial charge of atoms of the compound EC4

Atom	Partial Charge	Atom	Partial Charge
C3	0.513	C16	-0.117
O4	0.115	C17	0.239
C6	0.356	O18	-0.348
O7	-0.394	N19	0.056
O8	-0.253	C20	-0.106
C9	0.083	C21	-0.071
C10	-0.149	C22	-0.123
C11	-0.118	C23	-0.117
C12	-0.073	C28	0.229
C13	-0.129	O29	-0.411
C14	-0.084	N30	0.01
C15	-0.121	C31	-0.094

TABLE 9 : Partial charge of atoms of the compound EC5

Atom	Partial Charge	Atom	Partial Charge
C3	0.493	C16	-0.128
O4	0.108	C17	0.241
C5	-0.086	O18	-0.358
C6	0.354	N19	-0.004
O7	-0.39	C20	-0.1
O8	-0.257	C21	-0.074
C9	0.083	C22	-0.123
C10	-0.149	C23	-0.116
C11	-0.114	C24	-0.089
C12	-0.119	C28	0.229
C13	-0.137	O29	-0.396
C14	-0.058	N30	-0.012
C15	-0.12	C31	-0.091

TABLE 10 : Partial charge of atoms of the compound EC6

Atom	Partial Charge	Atom	Partial Charge
C3	0.497	C16	-0.117
O4	0.126	C17	0.235
C5	-0.062	O18	-0.371
C6	-0.139	N19	0.035
C7	0.11	C20	-0.071
C8	-0.178	C21	-0.15
O9	-0.182	C22	-0.051
C10	0.049	C23	-0.061
C11	-0.042	C28	0.225
C12	-0.11	O29	-0.49
C13	-0.109	N30	0.032
C14	-0.08	C31	-0.088
C15	-0.112		

TABLE 11 : Partial charge of atoms of the compound EC7

Atom	Partial Charge	Atom	Partial Charge
C3	0.368	C18	-0.117
O4	-0.168	C19	-0.113
C5	-0.047	C20	0.232
C6	-0.55	O21	-0.347
S7	2.243	N22	-0.01
O8	-0.695	C23	-0.085
O9	-0.513	C24	0.23
C10	-0.922	O25	-0.36
C11	0.039	N26	-0.018
C12	-0.144	C27	-0.089
C13	-0.191	C28	-0.056
S14	0.57	C29	-0.133
C15	-0.124	C30	-0.12
C16	-0.126	C31	-0.129
C17	-0.101	H32	0.146

TABLE 12 : Partial charge of atoms of the compound EC8

Atom	Partial Charge	Atom	Partial Charge
C3	0.362	C18	-0.116
O4	-0.181	C19	-0.119
C5	-0.071	C20	0.124
C6	-0.067	O21	-0.196
C7	-0.195	N22	0.362
C8	-0.089	C23	-0.14
C9	-0.088	C24	0.212
C10	-0.1	O25	-0.371
C11	-0.146	N26	0.022
C12	-0.06	C27	-0.09
C15	-0.097	C28	-0.082
C16	-0.113	C30	-0.098
C17	-0.084	C31	-0.071

TABLE 13 : Partial charge of atoms of the compound EC9

Atom	Partial Charge	Atom	Partial Charge
C3	0.335	C18	-0.115
O4	-0.174	C19	-0.122
C5	0.083	C20	0.107
O6	-0.239	O21	-0.202
C7	0.054	N22	0.356
C8	-0.125	C23	-0.144
C9	-0.13	C24	0.207
C11	-0.132	O25	-0.367
C12	-0.043	N26	0.024
C15	-0.115	C27	-0.093
C16	-0.094	N26	0.024
C17	-0.075	C27	-0.093

Full Paper

TABLE 14 : Partial charge of atoms of the compound EC10

Atom	Partial Charge	Atom	Partial Charge
C3	0.368	C16	-0.131
O4	-0.184	C17	-0.067
C5	-0.072	C18	-0.124
C6	-0.086	C19	-0.119
C7	-0.099	C20	0.105
C8	-0.125	O21	-0.207
C9	-0.132	N22	0.336
C10	-0.101	C23	-0.14
C11	-0.132	C24	0.207
C12	-0.043	O25	-0.364
C13	-0.095	N26	0.022
C14	-0.095	C27	-0.093
C15	-0.091		

A reference to TABLE 15 indicates that the compounds EC-1, EC-2, EC-6, EC-8, EC-9, EC-10 have maximum negative charge at carbonyl oxygen, the site being O-29, in EC-1, EC-2 and EC-6 and O-25 in EC-8, EC-9 and EC- 10. The presence of ester group in the molecule changes the situation, the site of maximum negative charge changes from carbonyl oxygen to ester oxygen. Such compounds are EC-3, EC-4 and EC-5. The site is O-7. In compounds EC-7, the highest value is at S= 0, the site is O-8. It is also evident that the highest negative charge is exhibited by sulphonyl oxygen, the value being -0.693, the ester groups are next highest which have values in between 0.39 to -0.404. The rest of the compounds have their values in between -0.353 to 0.49. All the inhibitors can be arranged in the following order in respect of their values

TABLE 15 : Partial charge on oxygen, nitrogen and hydrogen atoms

EC-1		EC-2		EC-3		EC-4		EC-5		EC-6	
Atom site	Partial charge	Atom site	Partial charge	Atom site	Partial charge	Atom site	Partial charge	Atom site	Partial charge	Atom site	Partial charge
O-18	-0.351	O-4	-0.185	O-4	-0.182	O-4	0.115	O-4	0.108	O-4	0.126
O-29	-0.353	N-8	0.269	O-7	-0.404	O-7	-0.394	O-7	-0.39	O-9	-0.182
O-4	-0.081	O-18	-0.206	O-8	-0.245	O-8	-0.253	O-8	-0.257	O-18	-0.371
N-19	0.006	N-19	0.38	O-18	-0.205	O-18	-0.348	O-18	-0.358	N-19	0.035
N-30	-0.051	O-29	-0.375	N-19	0.373	O-19	0.056	N-19	-0.004	O-29	-0.49
H-49	0.068	N-30	0.006	O-29	-0.36	O-29	-0.411	O-29	-0.396	N-30	0.032
H-58	0.112	H-53	0.112	N-30	0.032	N-30	0.01	N-30	-0.012	H-57	0.047
		H-61	0.112	H-51	0.11	H-49	0.09	H-51	0.085	H-55	0.085
				H-60	0.086	H-58	0.097	H-62	0.095		

EC-7		EC-8		EC-9		EC-10		Histidine	
Atom site	Partial charge	Atom site	Partial charge	Atom site	Partial charge	Atom site	Partial charge	Atom site	Partial charge
O-4	-0.168	O-4	-0.181	O-4	-0.174	O-4	-0.184	O-9	-0.39
O-8	-0.695	O-21	-0.196	O-6	-0.239	O-21	-0.207	H-19	0.043
O-9	-0.513	N-22	0.362	O-21	-0.202	N-22	0.336	H-20	0.043
O-21	-0.347	O-25	-0.371	N-22	0.356	O-25	-0.364	H-14	0.073
N-22	-0.01	N-26	0.022	O-25	-0.367	N-26	0.022		
O-25	-0.36	H-52	0.098	N-26	0.024	H-57	0.133		
N-26	-0.018	H-54	0.081	H-51	0.123	H-59	0.081		
H-48	0.095			H-53	0.082				
H-50	0.071								

of partial charges-

EC-7 > EC-6 > EC-4 > EC-3 > EC-5 > EC-2 > EC-8 > EC-9 > EC-10

The oxygen of sulphonyl has the highest negative charge, hence most favorable site for hydrogen bonding. Histidine has 20 atoms as shown in TABLE 1. The par-

tial charges on each atom have been evaluated and are included in TABLE 16. Nitrogens at site N-3, and N-11, have weak negative values hence are not the possible site for hydrogen bonding. The oxygen at site O-9 and O-10 have negative charge of the order 0.39 and 0.30 hence can play important role in hydrogen bonding. The partial charge on hydrogen atoms attached to nitrogen atoms of inhibitors (EC-1 to EC-10) and histidine are included in TABLE 15. The partial charges on H-19, H-20 and H-14 of histidine are lower than the partial charges on hydrogen atoms of inhibitors. This implies that hydrogen bonding will be between hydrogen of inhibitors and carbonyl oxygen (O-9) of hisitidine because it has higher negative partial charge (-0.392) than the negative charge on carbonyl oxygen of inhibitors (EC-1, EC-2, EC-5, EC-9 and EC-10). The negative partial charge on ester oxygen of EC-4 (O-7), EC-5 (O-7) on sulphonyl oxygen of EC-7 (O-8) and carbonyl oxygen of EC-6 (O-29) are higher as compared to negative charge on carbonyl oxygen(O-9) of histidine. It is most likely that hydrogen bonding in these cases involve hydrogen of histidine (H-14). Hence the hydrogen bondings are of two types: In one case the hydrogen of inhibitor and oxygen of histidine are involved and in other case where hydrogen of histidine and oxygen of inhibitors are involved. Both these types of hydrogen bonding are shown in TABLE 17 and TABLE 17A.

TABLE 16 : Partial charge of atoms of Histidene

Atom	Partial Charge	Atom	Partial Charge
C1	-0.309	C7	-0.071
C2	-0.134	C8	0.382
N3	-0.115	O9	-0.392
C4	-0.247	O10	-0.306
N5	0.317	N11	-0.034
C6	-0.04		

TABLE 17 : Hydrogen bonding between hydrogen of inhibitors and oxygen of histidine

Inhibitor	Atom site	Partial charge	Receptor	Atom site	Partial charge	Difference
EC-1	H-58	0.112	Histidine	O-29	-0.392	0.504
EC-2	H-61	0.112				0.504
EC-5	H-62	0.095				0.487
EC-8	H-52	0.098				0.490
EC-9	H-51	0.123				0.515
EC-10	H-57	0.133				0.525

Sequence: - EC-10>EC-9>EC-1>EC-2>EC-8>EC-5

TABLE 17A : Hydrogen bonding between hydrogen of histidine and oxygen of inhibitor

Receptor	Atom site	Partial charge	Inhibitor	Atom site	Partial charge	Difference
Histidine	H-57	0.123	EC-3	O-7	-0.404	0.527
			EC-4	O-7	-0.394	0.517
			EC-6	O-29	-0.490	0.613
			EC-7	O-8	-0.695	0.695

Sequence: - EC-7>EC-6>EC-3>EC-4

CONCLUSION

1. ΔN, ΔE, E_{int} and HOMO-LUMO gap indicate that EC-2 is the strongest and EC-3 is the weakest chelating agent.
2. Hydroxamates which have lower number of electrons and have lower value of electronegativity are better chelating agents
3. Two types of hydrogen bonding exist
   I. Hydrogen of histidine and oxygen of inhibitor are involved.
   II. Hydrogen of inhibitor and oxygen of histidine are involved.
4. Sulphonyl oxygens have the highest value of negative charge, next is oxygens of ester and the last is oxygens of carbonyl.
5. Most favorable site for hydrogen bonding is sulphonyl oxygen where partial charge is -0.695 and the hydrogen where partial charge is 0.133 or 0.123.

ACKNOWLEDGEMENT

The financial support of University Grants Commission, New Delhi, for this work is gratefully acknowledged.

REFERENCES

[1] R.G.Pearson; Coordination.Chem.Rev., **100**, 401 **(1990)**.
[2] Singh Divya, Ahmad Shahin, P.P.Singh; J.Mol.Stru.(THEOCHEM), **905**, 13 **(2009)**.
[3] A.J.R.Barrett, N.D.Rawling, J.F.Woessner, Eds.; Hand Book of proteolytic Enzymes, London: Academic Press, & references cited in, **(1998)**.

[4] H.J.Smith, C.Simons, Eds.; Proteinase & Peptidase Inhibitor – Recent Potential Targets for Drug Development, London: Taylor & Francis, **(2002)**.
[5] L.Tarko, S.Calafeteanu; Elect.J.Biomed., **2**, 22 **(2006)**.
[6] B.C.De, S.Pikul; Clin.Cancer Res., **5**, 3603 **(1999)**.
[7] P.M.O'Brein, D.F.Ortwine, A.G.Parlovsky; J.Med.Chem., **43**, 156 **(2000)**.
[8] M.G.Natchus, R.G.Bookland, M.J.Laufersweiler; J.Med.Chem., **44**, 1060 **(2001)**.
[9] R.G.Parr, R.G.Pearson; J.Am.Chem.Soc., **105**, 7512 **(1983)**.
[10] P.P.Singh, F.A.Pasha, H.K.Srivastava; QSAR & Combi.Sci., **22**, 843 **(2003)**.
[11] A.Berger, I.Schechter; **275**, 249 **(1970)**.
[12] D.Pei, T.Kang, H.Qi; J.Biol.Chem., **275**, 43 **(2000)**.
[13] M.Trexler, K.Briknarová, M.Gehrmann, M.Llinás, L.Patthy; J.Biol.Chem., **278**, 14 **(2003)**.
[14] O.Santos, C.D.Mc Dermott, R.G.Daniels, K.Appelt; Clin.Exp.Metas, **15**, 499 **(1997)**.
[15] R.Franke; Theoretical Drug Design Method, 123 **(1984)**.
[16] Z.Zhou, R.G.Parr; J.Am.Chem.Soc., **112**, 5720 **(1990)**.
[17] K.Fukui; Theory of Orientation and Stereoselection, Springer Verlag, New York, **(1975)**.
[18] I.Fleming; Frontier Orbital and Chemical Reaction, John Wiley & Sons New York, **(1976)**.
[19] F.A.Pasha, H.K.Srivastava, P.P.Singh; Mol.Diversity, **9**, 215 **(2005)**.
[20] H.R.Horton, Z.A.Moran, R.S.Ochs, J.D.Rawn, K.G.Scringear; Principle of Biochemistry, 2nd, Prontice: New Jersey, p36 and 152 **(1996)**.
[21] V.K.Sahu, A.K.R.Khan, R.K.Singh, P.P.Singh; Int.J.Qua.Chem., **109**, 1243 **(2009)**.
[22] T.Stams et al.; Struc.Biol., **1**, 119 **(1994)**.
[23] F.Grams et al.; Biochemistry., **34**, 14012 **(1995)**.