Quantitative Structure-Activity Relationship Studies on Some Series of Matrix Metalloproteinase Inhibitors

THESIS

Submitted in partial fulfilment
of the requirement for the degree of

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by

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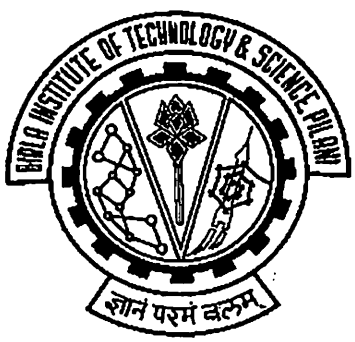
Under the Supervision of

Prof. S. P. GUPTA



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CERTIFICATE

This is to certify that the thesis entitled "**Quantitative Structure-Activity Relationship Studies on Some Series of Matrix Metalloproteinase Inhibitors**" and submitted by **KUMARAN S, ID. No. 2001PHXF409** for the award of Ph. D Degree of the Institute, embodies the original work done by him under my supervision.

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Date: 22.8.2005

Dedicated to My Mother, Father and God.

ॐ सह नाववतु । सह नौ भुनक्तु । सह वीर्य
करवावहै। तेजस्वि नावधीतमस्तु मा विद्विषावहै। ।
ॐ शान्तिः शान्तिः शान्तिः। ।

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Kumaran

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Abstract

Quantitative Structure Activity Relationship (QSAR) study has been carried out on several series of matrix metalloproteinase (MMP) inhibitors with the objective to investigate the physicochemical properties of these molecules which can make them selective for given enzyme and also to explore the mechanism of drug-receptor interactions, which could give a rationale to develop more specific and selective inhibitors. The following series of MMP inhibitors were subjected to the study:

1. Sulfonylated aminoacids and their hydroxamates
2. Functionalized 4-aminoproline hydroxamates
3. Anthranilic hydroxamic acid inhibitors
4. Bicyclic heteroaryl hydroxamic acid analogs
5. Pyranyl hydroxamic acid analogs
6. Piperidine sulfonamide aryl hydroxamic acid analogs
7. Acyclic hydroxamic acid analogs
8. Piperazine, Piperidine and Diazepine hydroxamic acid analogs
9. Benzodiazepine hydroxamic acid analogs

Majority of the QSAR results shows that the MMPs favor electronic interactions and in some cases hydrophobic interactions. In most of the cases the MMP-9 and MMP-13 have been shown to behave in a similar fashion with the inhibitors, suggesting that the mechanism of inhibition of these enzymes may be similar. For several series of MMP-1 inhibitors the inhibiting potency has been shown to have significant parabolic correlations with the hydrophobic property of the molecules suggesting that the mechanism of inhibition of MMP-1 by these inhibitors may be allosteric.

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LIST OF ABBREVIATIONS

ADAM	:	A disintegrin and a metalloprotease
B	:	Verloop's steric parameters (breath of substitutent)
BM	:	Basement Membrane
ChC	:	*Clostridium histolyticum* collagenase
ClogP	:	Calculated hydrophobicity
Eq. / Eqs.	:	Equation / Equations
ECM	:	Extra-Cellular Matrix
E_s	:	Steric constant
F	:	Fisher-ratio
IC	:	Isolating carbon
IC_{50}	:	Molar concentration of the compounds leading to the 50% inhibition of the enzymes
K_i	:	Enzyme inhibition constant
L	:	Verloop's steric parameters (length of substitutent)
LOO	:	Leave-One-Out method
MMP	:	Matrix metalloproteinases
MMPI	:	Matrix metalloproteinases inhibitors
MR	:	Molar refractivity
MSS	:	Musculoskeletal syndrome
MT1-MMP	:	Membrane-type MMPs
MV	:	Molar volume
N	:	Avogadro's number
n	:	Number of data points
NIC	:	Nonisolating carbon
P	:	Partition coefficient
Pol / α	:	Polarizability
QSAR	:	Quantitative structure-activity relationship
r	:	Correlation coefficient
r^2_{cv}	:	Square of cross-validated correlation coefficient

RA	:	Rheumatoid arthritis
ref.	:	Reference
S	:	E-state index
s	:	Standard deviation
TACE	:	TNF-α converting enzyme
TIMP	:	Tissue inhibitors of metalloproteinase
TNF-α	:	Tumor necrosis factor-α
V_w	:	van der Waals volume
WLN	:	Wiswesser line notation
δ^v	:	valence vertex connectivity
π	:	Hydrophobic constant
σ	:	Hammett constant
χ	:	Molecular connectivity index
${}^1\chi^v$	:	First-order valence molecular connectivity index

CHAPTER 1

INTRODUCTION
AND
REVIEW OF LITERATURE

1 Introduction

The matrix metalloproteinases (MMPs) are a family of structurally related zinc containing endopeptidases that degrade and remodel structural proteins in the extracellular matrix (ECM), basement membrane (BM), and connective tissues [1-3]. They include over 25 zinc-containing enzymes, such as collagenases, stromelysins, gelatinases and membrane-type MMPs and have been implicated in tissue remodeling at various stages of human development, wound healing, and disease. However, an imbalance caused by overexpression and activation of these MMPs result in tissue degradation, leading to a wide array of disease processes, such as osteoarthritis, rheumatoid arthritis, tumor metastasis, and a host of others [4-12]. Therefore, the study of the inhibition of MMPs has become of great interest.

Of the known human MMP enzymes, the ones of current therapeutic interest are fibroblast collagenase (MMP-1), neutrophil collagenase (MMP-8), collagenase (MMP-13), gelatinase A (MMP-2), gelatinase B (MMP-9), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), matrilysin (MMP-7), membrane-type-1-MMP (MT1-MMP), and aggrecanase. Although the development of MMP inhibitors started since the early 1980s, it has been greatly accelerated only recently since the three-dimensional crystal and the solution structures of the inhibitors bound to some of the MMPs, e. g., MMP-1, 3, 7, 8 and MT1-MMP could be studied only recently [13].

Since the researchers started taking interest in the development of MMP inhibitors, a number of compounds progressed into clinical trials for the cancer, rheumatoid arthritis, and osteoarthritis. Therefore, the study of the inhibition of MMPs has become of great interest and leads to development of broad spectrum MMP inhibitors, which in clinical experiences show intolerable side effects of musculoskeletal syndrome (MSS), that is due to the undesirable inhibition of MMP-1. Consequently, efforts have been made to investigate selective inhibitors of MMPs to develop molecules for specific diseases. Most of these broad spectrum inhibitors belong to different classes

of hydroxamates. Several research groups used the structure based design to modify these non-specific broad spectrum inhibitors to compounds that are more selective for specific MMPs that would be exploited for the safe, long term treatment of cancer, osteoarthritis and rheumatoid arthritis.

The objective of the research is to carry out quantitative structure-activity relationship (QSAR) studies on different series of matrix metalloproteinases inhibitors (MMPI), so as to investigate the physicochemical properties of these molecules which can make them selective for given enzyme and also to explore the mechanism of inhibition of these enzymes which can be exploited to develop drugs against variety of diseases.

1.1 REVIEW OF LITERATURE

1.1.1 Matrix Metalloproteinase

The extra-cellular matrix (ECM) plays a critical role for the structure and integrity of various tissue types in higher vertebrates [14,15]. The ECM have all kinds of structural proteins such as basement-membrane and interstitial collagens, fibronectin, vitronectin, enactin, laminin, versican, elastin, aggrecan, perlecan, tenascin, fibrinogen and proteoglycans [16,17]. These important structural proteins are degraded by a large family of zinc endopeptidases known as matrix metalloproteinases (MMPs), during normal physiological and physiopathological events such as embryonic development, blastocyst implantation, nerve growth, ovulation, morphogenesis, angiogenesis, tissue resorption, wound healing, bone remodeling, apoptosis, cancer invasion and metastasis, arthritis, atherosclerosis, aneurysm, skin ulceration, corneal ulceration, gastric ulcer and liver fibrosis [14,18-22]. However, their aberrant regulation leads them to become hyperactive that results in tissue degradation and a wide array of disease processes, such as osteoarthritis [23,24], rheumatoid arthritis [25-27] tumor metastasis [28-30], multiple sclerosis [31,32], congestive heart failure [33-35], chronic obstructive pulmonary disease (COPD) [36-39], and a host of others.

1.1.2 Structure and Function

At least 25 mammalian zinc-containing enzymes (Table 1.1) have been isolated till now and most of them share a significant sequence homology and can be subdivided according to the macromolecular substrate [40] requirements into: (1) collagenases (MMP-1, -8, -13 and -18); (2) gelatinases (MMP-2 and -9); (3) stromelysins (MMP-3, -10 and -11); and (4) membrane-type MMPs (MT-MMPs) (MMP-14, -15, -16 and -17). MMPs possess a modular structure [40-43] (Figure 1.1) consisting of:

(i) N-terminal signal peptide sequence (Pre in Figure 1.1) which direct MMPs to the secretory pathways.

Table 1.1. Human matrix metalloproteinases and their substrates [40]

MMPs	Protein	Principal substrate(s)	Preferred scissile amide bond
MMP-1	Collagenase-1	fibrillar and nonfibrillar collagens (types I, II, III, VI and X),gelatins	Gly-Ile
MMP-2	Gelatinase A	basement membrane and nonfibrillar collagens (types IV, V, VII, and X), fibronecin, elastin	Ala-Met
MMP-3	Stromelysin-1	proteoglycan, laminin, fibronectin, collagens (type III, IV, V, IX), gelatins; pro-MMP-1	Gly-Leu
MMP-7	Matrilysin	fibronectin, gelatins, proteoglycans	Ala-Ile
MMP-8	Collagenase-2	fibrillar collagens (type I, II, III)	Gly-Leu; Gly-Ile
MMP-9	Gelatinase B	basement membrane collagens (type IV, V), gelatins	Gly-Ile; Gly-Leu
MMP-10	Stromelysin-2	fibronectins, collagens (type III, IV) gelatins, pro-MMP-1)	Gly-Leu
MMP-11	Stromelysin-3	serpin	Ala-Met
MMP-12	Macrophage metalloelastase	elastin	Ala-Leu, Tyr-Leu
MMP-13	Collagenase-3	fibrillar collagens (type I, II, III), gelatins	Gly-Ile
MMP-14	MT1-MMP	pro-72 kDa gelatinase	not determined
MMP-15	MT2-MMP	proMMP-2, gelatin, fibronectin, tenascin, nidogen, laminin	not determined
MMP-16	MT3-MMP	pro-72 kDa gelatinase	not determined
MMP-17	MT4-MMP	not determined	Ala-Gly
MMP-18	Collagenase-4 from Xenopus	not determined	Gly-Ile
MMP-19	Stromelysin-4	gelatin	not determined
MMP-20	Enamelysin	amelogenin (dentinc), gelatin	not determined
MMP-21	XMMP from Xenopus	not determined	not determined
MMP-22	CMMP from chicken	gelatin, casein	not determined
MMP-23	CA-MMP (Cysteine Array)	not determined	not determined
MMP-24	MT5-MMP	proMMP-2, proMMP-9, gelatin	not determined
MMP-25	MT6-MMP	collagen IV, gelatin, fibronectin, fibrin	not determined
MMP-26	Endometase	Collagen IV, fibronectin, fibrinogen, gelatin, proMMP-9	not determined
MMP-27	-	not determined	not determined
MMP-28	Epilysin	casein	not determined

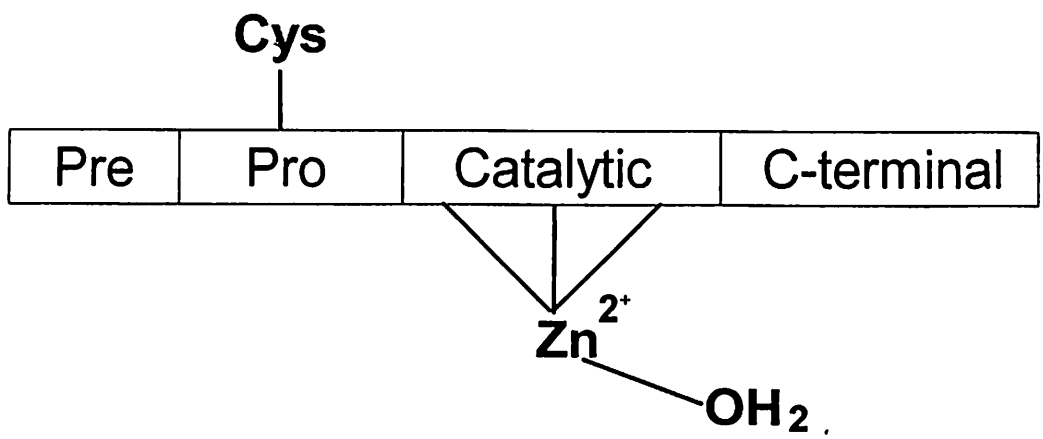


Figure 1.1. Schematic representation of the structure of a typical MMP enzyme [43]

(ii) Propeptide domain (Pro in Figure 1.1) which has a conserved Cys residue that is coordinated to the catalytic Zn(II) ion. This prevents the autolysis of these highly active enzymes and confers latency to the enzymes.

(iii) Catalytic domain consists of 170 amino acid residues. They contain a highly conserved zinc binding motif, consisting of three histidine residues and a conserved glutamate, important in catalysis. The Zn(II) binding motif is HEXXHXXGXXH (where X can be any amino acid residue).

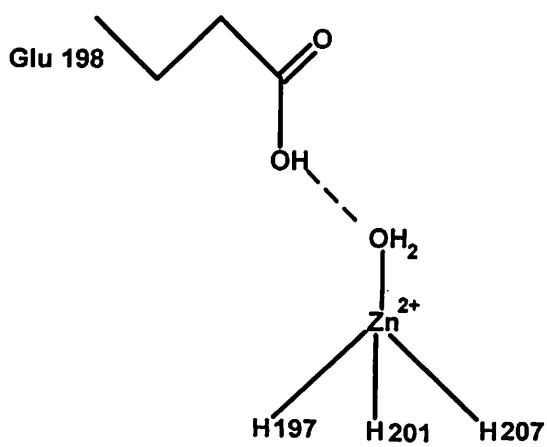
(iv) C-terminal domain which is essential for the recognition of macromolecular substrates and serves to anchor the enzymes to the cell membrane.

(v) Metal ions like Zn(II) and Ca(II) ions. All MMPs contain two Zn(II) and two to three Ca(II) ions. One of the zinc ions, coordinated by three histidines belonging to the binding motif is critical for catalysis. The fourth ligand being a water molecule coordinated to Zn(II) in a quasi tetrahedral geometry, acts as the nucleophile during the proteolytic process. The other zinc ion and the calcium ions have a structural role in stabilizing the enzyme from autocleavage [40,41].

1.1.3 Catalytic and Inhibition Mechanism

The active site of MMPs has Zn(II) ion coordinated to three histidine residues (H197, H201, H207) and water molecule as fourth ligand. The zinc-bound water molecule interacts with the carboxylate moiety of the conserved glutamate (Glu 198 in MMP-8), probably forming a hydrogen bond with it (Figure 1.2) [44]. Thus, a very effective nucleophile is formed again, which will attack the amide scissile bond.

The proteolytic mechanism of MMPs involves the binding of the substrate with its scissile carbonyl moiety weakly coordinated to the catalytic Zn(II) ion (Figure 1.3 A), followed by nucleophilic attack of the zinc-bound (and glutamate hydrogen-bonded) water molecule on this carbon atom (Figure 1.3 B). The water molecule donates a proton to the carboxylate moiety of Glu 198, which transfers it to the nitrogen atom of the scissile amide bond (Figure 1.3 C). Then, the Glu 198 residue transfers the second remaining proton of the water to the nitrogen of the scissile amide bond, resulting in



MMP-8

Figure 1.2. Coordination of the Zn(II) ion within the active sites of matrix metalloproteinase-8 (MMP-8) [44]

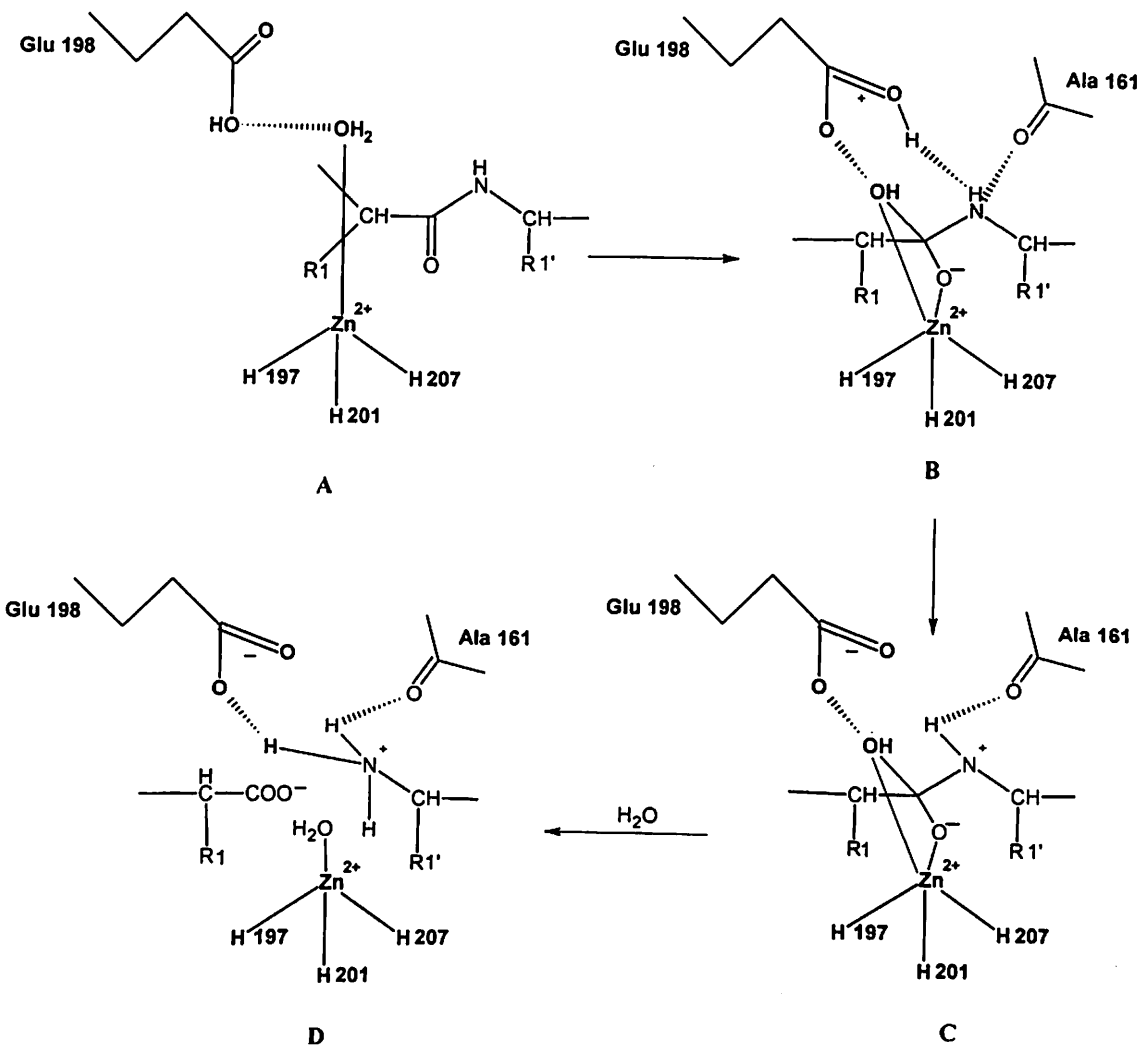


Figure 1.3. Catalytic mechanism of MMPs (exemplified for MMP-8) [44]

peptide bond cleavage (Figure 1.3 D). During these processes, the Zn(II) ion stabilizes the developing negative charge on the carbon atom of the scissile amide bond, whereas a conserved alanine residue (Ala 161 in MMP-8) helps to stabilize the positive charge at the nitrogen atom of the scissile amide [42-44].

1.2 Matrix Metalloproteinase Inhibitors

Two major endogenous inhibitors for MMPs are tissue inhibitors of metalloproteinases (TIMPs) and α_2-macroglobulin [45]. Their action on MMPs includes inhibition of catalytically active forms of the enzymes and prevention or delay of conversion of proMMPs to their active forms through negative feedback mechanism.

Several synthetic inhibitors have been recently developed where the inhibition of MMPs is correlated with binding of the inhibitor molecule to the catalytic metal ion, with or without substitution of the metal bound water molecule. Depending on the zinc-binding function contained in their molecule, matrix metalloproteinase inhibitors (MMPIs) belong to several chemical classes, such as carboxylates, hydroxamates, thiols, phosphorus-based inhibitors, sulfodiimines, etc. The strongest inhibitors are generally the hydroxamates which bind bidentately to the catalytic Zn(II) ion of the enzyme, which in this way acquires a distorted trigonal bipyramidal geometry, as shown by X-ray crystallography [45]. The hydroxamate anion forms a short and strong hydrogen bond with the carboxylate moiety of Glu 219 that is oriented towards the unprimed binding regions. The NH hydroxamate also forms a hydrogen bond with the carbonyl oxygen of Ala 182 [46,47]. Thus, several strong interactions are achieved at the zinc site without any significant unfavorable contacts (Figure 1.4).

Based on the nature of the S_1' pocket binding pockets MMPs are classified into two main types: (1) the deep pocket enzymes (such as MMP-2, MMP-3, MMP-8, MMP-9 and MMP-13), possessing a relatively big S_1' pocket; and (2) the shallower pocket enzymes (MMP-1, MMP-7 and MMP-11 among others) which possess a somehow smaller specificity S_1' pocket due to its partial occlusion by bulkier amino acid residues,

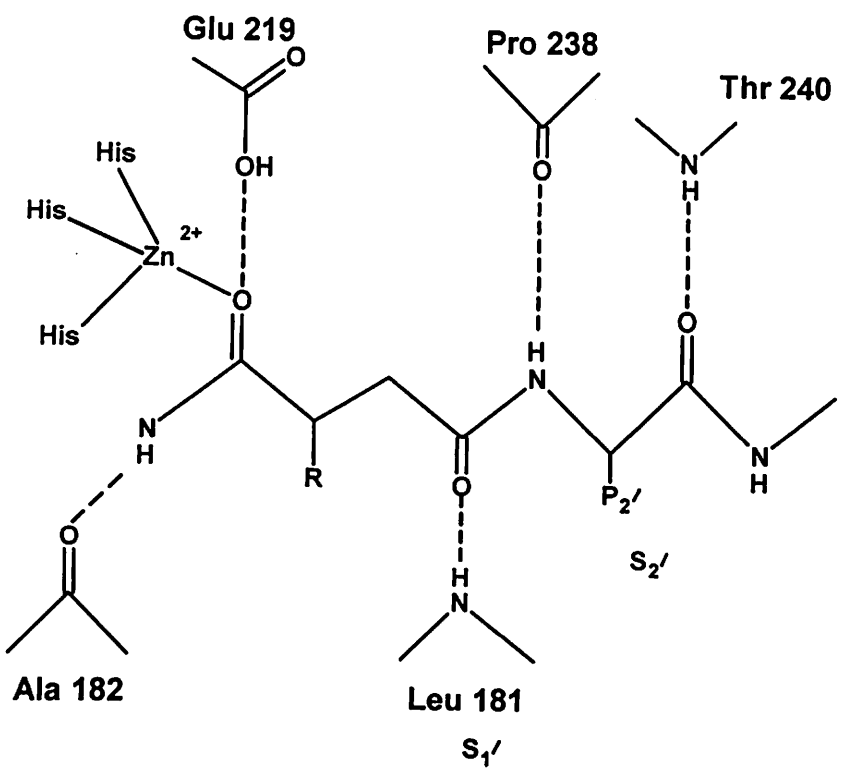
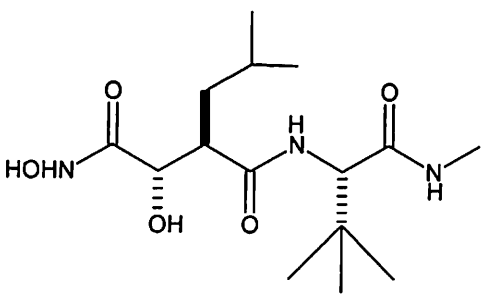


Figure 1.4. Binding of a hydroxamate inhibitor to MMP-7 as determined by x-ray crystallography [47]

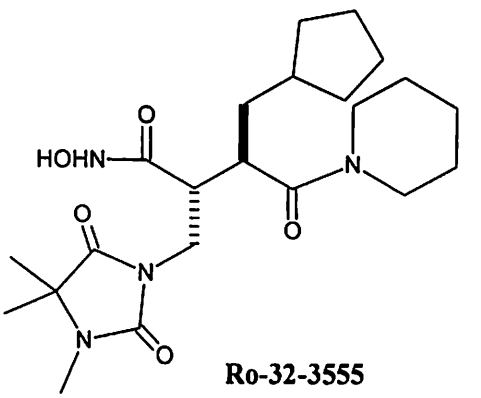
such as that in position 193 (MMP-8 numbering) which from Leu in MMP-8, becomes Arg in MMP-1, Tyr in MMP-7 and Gln in MMP-11 [48]. The S_2' and S_3' subsites are also important for the binding of inhibitors as well as for the specificity of such inhibitors towards different MMPs. This S_2' subsite is a solvent-exposed cleft with a general preference for hydrophobic P_2' residues in both substrates and MMPIs. The S_3' subsite on the other hand is a relatively ill-defined, solvent exposed region [48,49].

Most investigated class of MMPIs are hydroxamates. Thousands of structural variants containing the CONHOH moiety have been synthesized and assayed as inhibitors of MMPs and other types of metallo-enzymes. These hydroxamates are generally classified on the basis of the attachment of CONHOH moiety to the main scaffold [50]. So they can be aryl hydroxamates (having aryl scaffold attached to CONHOH moiety), non-aromatic hydroxamates (having piperidine, piperazine, benzodiazepine, diazepine scaffolds attached to CONHOH moiety) and acyclic hydroxamates (having acyclic scaffolds attached to α-carbon of the CONHOH moiety).

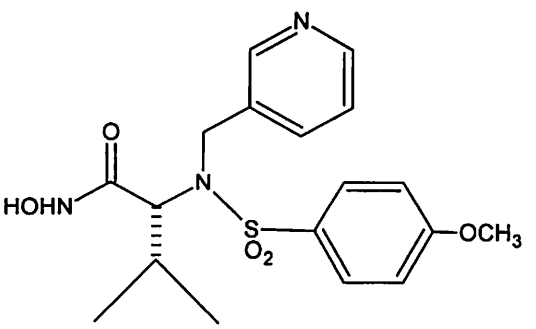
As the study of the inhibition of MMPs has become of great interest thereby leading to development of broad spectrum hydroxamate based MMP inhibitors like marimastat, Ro-32-3555, CGS-27023A and AG-3340 (Figure 1.5). However the clinical experiences of these molecules show intolerable side effects of musculoskeletal syndrome (MSS) which is due to the undesirable inhibition of MMP-1 [51]. Therefore, recently the efforts have been made to selectively inhibit the MMPs to develop molecules for specific diseases. The selective inhibition of MMP-13 [52] and aggrecanase [53] over MMP-1 may have therapeutic benefit in osteoarthritis without causing MSS side effects. The MMP-2 and MT1-MMP have a role in angiogenesis and human tumors [54], and MMP-7 has its role in colonic adenocarcinomas [55]. Similarly MMP-3 and MMP-9 play the role in invasive mesenchymal like tumors [56-58]. So the specific inhibition of the MMP-2, -3, -7, -9 and MT1-MMP would be a valuable target for cancer treatment.



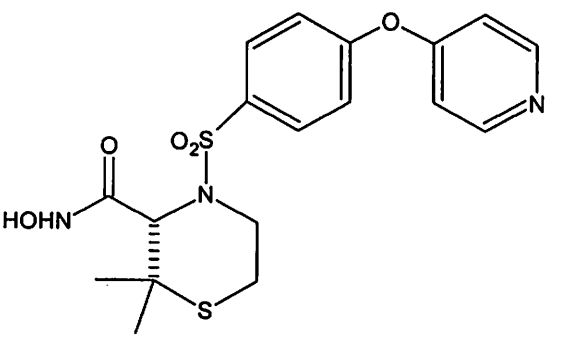
Marimastat



Ro-32-3555



CGS-27023A



AG-3340

Figure 1.5. Some important MMP inhibitors in clinical trials

1.2.1 Tumor Necrosis Factor-α Converting Enzyme (TACE) Inhibitors

TACE (TNF-α converting enzyme, TNF: tumor necrosis factor) is a member of the adamalysin/reprolysin subfamily contained within the metzincin superfamily, which also includes the MMPs. TACE is structurally categorized into the ADAM (a disintegrin and a metalloprotease) family, but its catalytic site is quite similar to that of MMPs [59].

TNF-α is one of the major pro-inflammatory cytokines normally produced by mononuclear cells in response to immunostimuli to protect against infection, tissue destruction, and tumors [60]. TNF-α is initially produced as a membrane bound 26 kDa propeptide on the cell surface. This membrane bound form of pro-TNF-α is processed to 17 kDa soluble form of mature TNF-α by a zinc endopeptidase called TNF-α converting enzyme (TACE) [61,62]. The process of the release of mature TNF-α from cell surface is called as shedding of TNF-α which plays a crucial role in mediation of several inflammatory events within the body. However, when over-produced, it initiates a cascade of other agents including interleukin-1 and interleukin-6 that have been linked to several diseases including rheumatoid arthritis [63], Crohn's diseases [64] and psoriasis [65].

The success of currently marketed biologics targeting TNF-α, etanercept (Enbrel^{TM}), and infliximab (Remicade^{TM}), has clearly implicated the role of TNF-α in rheumatoid arthritis, and the other therapeutic indications. However, these two biologics are orally inactive and have a long half-life in the body that cause allergic reactions and the neutralization of antibody productions [66]. So there has been a great deal of interest in the design of small molecule inhibitors of TACE along with MMPs in order to suppress the amount of circulating TNF-α to develop molecules that could be useful for treatment of variety of disorders.

1.2.2 Bacterial Collagenases Inhibitors

Like MMPs, there are also other enzymes, such as bacterial collagenase, that degrade ECM. *Clostridium histolyticum* collagenase (EC 3.4.24.3), abbreviated as ChC, is one of the bacterial collagenases, isolated from *Clostridium histolyticum*. It is a 116 kDa zinc-protein, belonging to M-31 metalloproteinase family [67], that is able to hydrolyze triple helical regions of collagen under physiological conditions as well as an entire range of synthetic peptide substrates [68-73].

In fact, the crude homogenate of *C. histolyticum*, which contains several distinct collagenase isozymes, is the most efficient system known for the degradation of connective tissue, being also involved in the pathogenicity of this and related clostridia, such as *C. perfringens*, which causes human gas gangrene and food poisoning among others [74,75].

Similar to the mammalian MMPs, ChC incorporates the conserved HEXXH zinc-binding motif, which in this specific case is His^{415}-EXXH, with the two histidines (His 415 and His 419) acting as Zn(II) ligands, whereas the third ligand seems to be Glu 447, and a water molecule/hydroxide ion acts as nucleophile in the hydrolytic scission.

Like MMPs, the ChC is also a multiunit protein. Both of them are considered to have similar mechanism of action for the hydrolysis of proteins and synthetic substrates [67,68,71,72,75,76]. Therefore it was hypothesized that hydroxamates which strongly inhibit MMPs would also act as potent ChC inhibitors. *C. histolyticum* collagenase cause so much damage and so quickly that antibiotics are ineffective. Inhibition of this enzyme is necessary for the treatment of bacterial corneal keratitis, a serious ocular infection which usually lead to loss of vision.

1.3 Quantitative Structure-Activity Relationship Studies

Over the past two decades, the intellectual focus of medicinal chemistry has shifted dramatically from how to make a molecule, to what molecule to make. The lead molecule, as we know, is a prototype compound that has the desired biological or pharmacological activity, but may have undesirable characteristics such as toxicity, other biological activities, insolubilities or metabolic problems. Early structure-activity relationship (SAR) studies (prior to 1960s) simply involved the synthesis of as many analogues as possible of the lead and then testing to determine the effects of structure on activity, based on the assumption the biological activity is a function of its chemical structure.

Today biological or therapeutic activity is considered to be a function of physicochemical properties. With this concept, structure-activity relationships are developed, when a set of physicochemical properties of a group of congeners is found to explain the variations in biological response of these compounds. This has resulted in the discovery, examination, and interpretation of structure-activity relationships in a more systematic way, which has led to the introduction of quantitative structure-activity relationship (QSAR) studies.

Since its inception in 1962 by Corwin Hansch's classic work, QSAR in biochemistry and biology has progressed steadily [77,78]. However, the advent of 3-D molecular graphics early in the 1980's in Langridge's Laboratory in the University of California, at Sanfrancisco, an explosive growth began to occur in methodology [79-85]. The attractive 3-D pictures of ligands bound to enzymes of enzymes of established structure captured researches attention, but mechanism based on physical organic chemistry was forgotten. This is not meant to downgrade graphics. Indeed graphics can be of enormous help if it is based on QSAR and receptors whose structure are known.

The development of automated synthesis capability along with the formulation of combinatorial chemistry approach has enabled the rapid synthesis of a large number of

molecules. This large increase in synthetic capacity has been accompanied by the automation of *in vitro* bioassays affording high throughput screening systems capable of generating massive amounts of data in a relatively short period of time. The combinatorial possibilities of this strategy for even simple systems can be explosive. The alternative to this labor intensive approach to compound optimization is to develop a theory that quantitatively relates variations in the biological activity to changes in the molecular descriptors which can easily be obtained for each compound. A Quantitative Structure-Activity Relationship can then be utilized to help guide chemical synthesis.

The correlation of molecular structure with biological activity is at the heart of modern medicinal chemistry, being fundamental both to our understanding of how drugs act, and to the rational design of more effective analogues. Over the last few decades, considerable advances have been made in studies of structure-activity relationship, largely because of the trend of towards expressing all aspects of "structure" in quantitative terms relative to standard. The most significant contributions to this endeavor have been made by Hansch and co-workers [86-88].

The quantitative approach to understanding drug action depends upon the ability to express structure by numerical values and then to relate these values to corresponding changes in activity. The response is going to be determined by the structure, i.e., by the physicochemical properties of the compound, and within a closely related or so-called congeneric series of compounds, changes in structure can be related to changes in biological activity.

The QSAR study tries to explain the reasons of observed variations in biological activates of a group of congeners in terms of molecular modifications or variations caused by the changes by the change of substituents. The QSAR studies generally have two important aspects: predictive aspect and diagnostic aspect. The predictive aspect, as the name implies, deals with the extrapolation and interpolation of a correlation study to identify synthesis of more active derivatives and to avoid the synthesis and testing of derivatives of same or equivalent activity, minimizing the time needed to find a better

derivative. The diagnostic aspect, on the other hand, answers the mechanistic aspects of the relation, i.e., it helps obtain the information about the type of binding forces involved and about the mode of action of drugs. Results of both these aspects can lead to tailor-made design of new drugs of better activity with lesser or no side effects.

Some important approaches used in QSAR studies are the nonparameteric methods like Free-Wilson approach [89] or Fujita-Ban approach [90], the parametric method developed by Hansch [86-88], discriminant analysis [91], and the pattern recognition technique [92,93]. Various factors such as quality of the biological data, number of compounds tested, degree of variance in the results, and ratio of the time required for synthesis and biological testing dictate the choice of approach for the QSAR study.

The most popular and widely used approach continues to be the so called Hansch approach [86-88], where the variance in biological effect (ΔBE) is explained by the variance in certain linear free-energy related substituent constants which describe the changes in lipophilic/hydrophilic (ΔL/ΔH), electronic (ΔE), steric (ΔS), and other properties of the parent molecule induced by the substituents. This model can be expressed as follows:

$$\Delta BE = f(\Delta L/\Delta H, \Delta E, \Delta S, ...) \qquad (1.1)$$

The lipophilicity of a molecule can be described by the logarithm of partition coefficient P, measured in octanol-water system [94]. The change in lipophilicity or hydrophobicity due to a substituent is described by the lipophilic or hydrophobic constant π of the substituent defined as $\pi = \log P_X - \log P_H$, where X refers to the substituted derivative and H to the parent compound [95]. Lipophilicity can also be described by R_m values obtained from reverse-phase chromatography and by log k obtained from High Pressure Liquid Chromatography (HPLC). The change in electronic properties can be expressed by Hammett constant (σ) [96], charge densities, spectroscopic properties like chemical shift from IR or UV spectra, field constant (F), and resonance constant (R). The

steric influence of the substituents can be described by the Taft steric constant (E_s) [97], molar volume (MV), and molar refractivity (MR) [98,99].

Besides, many a drug activities have been found to depend exclusively upon the molecular size [100-106,108,109], which can be described by the van der Waals volume (V_w), and upon molecular graph, which is delineated by molecular connectivity index (χ) [110]. In addition to these, Verloop's [107] width parameters B and length parameter L, evaluated by measuring dimensions of substituents in a restricted number of directions with the aid of a computer program called STERIMOL, were also found to be useful in QSAR study. These parameters in their dimensional nature are indicative of the deviations of a substituent from spherical shape and their use might provide a better understanding of steric requirements in ligand-receptor interactions. In the present thesis, an extensive use has been made of these parameters.

In a stepwise linear multiple regression analysis, the biological activity (BA) can be related to various physicochemical, electronic, and steric parameters as:

$$BA = a\,\pi \text{ (or } \log P) + b\,\pi^2 \text{ (or } [\log P]^2) + c\sigma + dE_s + k \qquad (1.2)$$

where a, b, c and d are the regression coefficients and k the intercept obtained by least square method. Biological activity can be expressed by negative logarithm of the concentration of drug leading to a desired response. This reciprocal of the concentration used reflects the fact that greater potency is associated with a lower dose. Equation (1.2) shows a nonlinear, i.e., a parabolic dependence of activity on the hydrophobic character of molecules. Actually, Hansch had assumed a "random walk" of the molecules, where hydrophilic molecules tend to remain in aqueous phase, while hydrophobic molecules tend to go into lipid phase.

Only those molecules that have an optimal hydrophilic/hydrophobic balance tend to reach their goal in reasonable time and concentration. The nonlinear dependence of activity on π or log P value in an *in vivo* system is due to the nonlinear dependence of the

rate constant of drug transport thorough aqueous and bio-organic phases on lipophilicity, whereas in *in vitro* systems, such as enzyme inhibition, such nonlinear relationships result from equilibrium distribution of the drug toward different areas at the enzyme surface, from limited binding space at the active site, or from limited solubility of more lipophilic congeners.

However, in many cases the relationships between activity and lipophilicity were found to be strictly linear [86-88] and although the parabolic model proved to be extremely useful for practical purposes, there was an inconsistency between it and the linear model. Although much less is known about the dependence of biological activities on lipophilic character beyond the point of optimal lipophilicity (log P_o or π_o), most often a linear relationship is observed with a negative-slope beyond it. To overcome such inconsistencies between the linear and nonlinear models, a number of different models [111-117] were proposed, out of which Kubinyi's bilinear model was found, after Hansch's parabolic model, to be the most useful model [118-124] to describe the nonlinear relationships.

An alternative method, Free and Wilson analysis, is useful in systems in which the series of analogues are substituted at different positions. A Hansch treatment of such a series is complicated by the large number of physicochemical constants to be investigated. The additive model of Free and Wilson gives the relationship between biological activity and the presence or absence of a substituent was then expressed by the following equation:

$$\text{Activity} = A + G_{ij}A_{ij} \qquad (1.3)$$

where A was defined as the average biological activity for the series, G_{ij} the contribution to activity of a functional group i in the jth position and X_{ij} the presence (1.0) or absence (0.0) of the functional group i in the jth position.

In the Free-Wilson treatment, hydrogen is treated as a substituent. The intercept of the resulting model does not represent the activity of the unsubstituted parent structure, but merely an average of biological activities of all compounds in the series.

In the Fujita and Ban analysis, a modified version of the Free-Wilson treatment, the H-substituent value at each position is set equal to zero. This is just a linear transformation of the Free-Wilson equation performed by subtracting the H-substituent value from each substituent constant, at that position, and adding the same value to the intercept. The intercept now represents the activity of the parent structure.

1.3.1 Applications of QSAR in Drug Design

After formulation of a statistically significant as well as physicochemically meaningful correlation equation for a given set of compounds, the informations contained in the equation can be used to design new compounds. According to the method of utilization of the informations, examples could be classified into at least three categories:

(i) *Extrapolation of certain parameters leading to the maximum potency*
As the correlation may or may not be linear, the best way this can be done is to gradually extend the extrapolation until the maximum potency is generated.

(ii) *Identification of optimum structures with respect to certain parameters*
If a parabolic dependence of the activity on certain parameters is revealed, the structure can be optimized by being modified so that the value of the parabolic parameter term is close to the maximum. This way, the best compound in the series can be identified and depending on this one could make a decision to continue or discontinue the synthetic program

(iii) *Transposition of QSAR informations to other series of compounds*
The QSAR informations derived from a set of compounds A-$X_{1\sim n}$, prepared mainly on the basis of introduction or replacement of substituents, can be utilized to design new structures, A-X_m, where A is the basal skeletal structure that is kept unchanged and X means variable substituents or substructures.

A number of examples can be quoted where various combinations of the above points have been utilized to design compounds actually exhibiting the predicted activity.

1.3.2 Limitations of QSAR

Though QSAR studies can be successfully utilized to predict the activity of new analogues and discuss the mechanisms of drug-receptor interactions, they have some drawbacks and limitations as described below [125].

The substituent effect on hydrophobicity is characterized by logP based on an octanol-water system; hence, even a very significant correlation can not represent a true model for hydrophobic interaction between a drug molecule and the receptor. The value of logP also depends on the electronic characters and the hydrogen bonding properties of the substituents [121-126]. Thus, if one gets a correlation with logP only, one cannot conclude that there is only hydrophobic interaction between drug and receptor and that no electronic interaction or hydrogen bonding takes place. Another factor that may influence logP values is steric effect that can prevent the access of water to a hydrophilic group [127]. Steric interactions are extremely difficult to extrapolate from system to system. The use of parameters like MR, MW, V_w, etc., do not give any idea in what way steric effects would effect the drug-receptor interaction. A more serious problem arises with the electronic parameters. The Hammett constants do not reflect which portion of the drug molecule would be actually involved in the interaction with the receptor. Quantum mechanical calculations can provide some help in this, but they are time consuming and expensive.

Although molecules are represented as rigid structures on paper, they may in fact, be quite different in solution and their dynamic nature should be recognized. There is considerable evidence that macromolecules, even in crystalline state, exhibit a wide spectrum of motions [128-132]. These motions may be involved in some molecular conformational changes on substrate or group binding. Both drugs and biomolecules are

three dimensional objects whose chemical features are related to their three dimensional structures. The interaction between them involves a complementarity or fit between the two objects. Even a successful QSAR study will provide only indirect information about the three-dimensional aspects of drug-biomolecule interaction

Many structural features that affect the activity but can not be parameterized by the usual variables like π, σ, E_s, etc., are accounted for by the use of indicator variables. These indicator variables are arbitrarily assigned two values: one to indicate the presence of the specific structural feature and other to indicate its absence. If the entire series of congeners is divided into two sets, one with and one without the specific structural feature, one would obtain two equations, almost parallel, to each other, with a difference in their intercepts only. An indicator variable thus can be pictured simply as a constant that adjusts two parallel equations into one. If two sets are far apart in data space described by the usual parameters, one builds in a large amount of variance with the indicator variable leading to a much higher correlation coefficient (r) [133]. Despite the better 'r', the new correlation may be a poorer one, and thus, one can be misled if other statistical parameters are not available.

Another serious problem in QSAR analysis is the problem of collinearity. For example π and MR most often turn out to be so collinear that it becomes impossible to tell whether one or both are involved in SAR [134]. Over and above all, a QSAR study may be incorrectly interpreted if the biological property of interest is not correctly measured. A measured biological response maybe a complex result of several processes, and an *in vitro* model of drug-receptor interaction does not always represent the true *in vivo* model.

References

[1] Skiles, J. W., Gonnella, N. C. and Jeng, A. Y. *The design, structure, and therapeutic application of matrix metalloproteinase inhibitors, Curr. Med. Chem.*, *8*, 425-474 (**2001**).

[2] Skiles, J. W., Gonnella, N. C. and Jeng, A. Y. *The design, structure, and clinical update of small molecular weight matrix metalloproteinase inhibitors, Curr. Med. Chem.*, *11*, 2911-2977 (**2004**).

[3] Sepper, R., Konttinen, Y. T., Ding, Y., Takagi, M. and Sorsa, T. *Human neutrophil collagenase (MMP-8), identified in broncieclasis BAL fluid, correlates with severity of disease, Chest, 107*, 1641-1647 (**1995**).

[4] Shalinsky, D. R., Brekken, J., Zou, H., McDermott, C. D., Forsyth, P., Edwards, D., Margosiak, S., Bender, S., Truitt, G. and Wood, A. *Broad antitumor and antiangiogenic activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology trials, Ann. NY. Acad. Sci., 878*, 236-270 (**1999**).

[5] Taraboletti, G., Garofalo, A., Belotti, D., Drudis, T., Borsotti, P., Scanziani, E., Brown, P. D. and Giavazzi, R. *Inhibition of angiogenesis and murine haemoangioma growth by batmiastat, a synthetic inhibitor of metalloproteinases, J. Natl. Cancer Inst., 87*, 293-298 (**1995**).

[6] Lewis, E. J., Bishop, J., Bottomley, K. M. K., Bradshaw, D., Brewster, M., Broadhurst, M. J., Brown, P. A., Budd, J. M., Elliott, L. and Greenham, A. K. *Ro32-3555, an orally active collagenase inhibitor, prevents cartilage breakdown in vitro and in vivo, Br. J. Pharmacol., 121*,540-546 (**1997**).

[7] Bigg, H. F. and Rowan, A. D. *The inhibition of metalloproteinases as a therapeutic target in rheumatoid arthritis and osteoarthritis, Curr. Opin. Pharmacol., 1*, 314-320 (**2001**).

[8] Clark, I. M., Powell, L. K., Ramsey, S., Hazleman, B. L. and Cawston, T. E. *The measurement of collagenase, tissue inhibitor of metalloproteinases (TIMP), and collagenase-TIMP complex in synovial fluids from patients with osteoarthritis and rheumatoid arthritis, Arthritis Rheum., 36*,372-379 (**1993**).

[9] Mort, J. S., Dodge, G. R., Roughley, P. J., Liu, J., Finch, S. J., DiPasquale, G. and

Poole, A. R. *Direct evidence for active metalloproteinases mediating matrix degradation in interleukin 1-stimulated human articular cartilage*, *Matrix*, *13*, 95-102 (**1993**).

[10] Dodge, G. R., Pidoux, I. and Poole, A. R. *The degradation of type II collagen in rheumatoid arthritis: An immunoelectron microscopic study*, *Matrix*, *11*, 330-338 (**1991**).

[11] McCachren, S. S. *Expression of metalloproteinases and metalloproteinase inhibitor in human arthritic synovium*, *Arthritis Rheum.*, *34*, 1085-1093 (**1991**).

[12] Billinghurst, R. C., Dahlberg, L., Ionescu, M., Reiner, A., Bourne, R., Rorabeck, C., Mitchell, P., Hambor, J., Diekmann, O. and Tschesche, H. *Enhanced cleavage of type II collagen by collagenases in osteoarthritic articular cartilage*, *J. Clin. Invest. 99*, 1534-1545 (**1997**).

[13] Bode, W., Fernandez-Catalan, C., Tschesche, H., Grams, F., Nagase, H. and Skos, K. *Structural Properties of Matrix Metalloproteinases*, *Cell Mol. Life Sci.*, *55*, 639-652 (**1999**).

[14] Whittaker, M., Floyd, C. D., Brown, P. and Gearing, A. J. H. *Design and therapeutic application of matrix metalloproteinase inhibitors*, *Chem. Rev.*, 99, 2735-2776 (**1999**).

[15] Tschesche, H. *Human neutrophil collagenases*, *Methods Enzymol.*, *248*, 431-449 (**1995**).

[16] Leung, D., Abbenante, G. and Fairlie, D. P. *Protease inhibitors: Current status and future prospects*, *J. Med. Chem.*, *43*, 305-341 (**2000**).

[17] Babine, R. E. and Bender, S. L. *Molecular recognition of protein-ligand complexes: Applications to drug design*, *Chem. Rev.*, *97*, 1359-1472 (**1997**).

[18] Nagase, H. *Activation mechanisms of matrix metalloproteinases*, *Biol. Chem.*, *378*, 151-160 (**1997**).

[19] Nagase, H. and Woessner, J. F. Jr. *Matrix metalloproteinases*, *J. Biol. Chem.*, 274, 21491-21494 (**1999**).

[20] Bottomley, K. M., Johnson, W. H. and Walter, D. S. *Matrix metalloproteinase inhibitors in arthritis*, *J. Enzyme Inhib.*, *13*, 79-101 (**1998**).

[21] Dioszegi, M., Cannon, P. and Van Wart, H. E. *Vertebrate collagenases*, *Methods*

Enzymol., 248 , 413-431 (**1995**).

[22] Johnson, L. L., Dyer, R. and Hupe, D. J. *Matrix metalloproteinases, Curr. Opin. Chem. Biol., 2*, 466-471 (**1998**).

[23] Cawston, T. E. *Metalloproteinase inhibitors and the prevention of connective tissue breakdown, Pharmacol. Ther., 70*, 163-182 (**1996**).

[24] Blaser, J., Triebel, S., Maajosthusmann, U., Rimisch, J., Krahlmateblowski, U., Freudenberg, W., Fricke, R. and Tschesche, H. *Determination of metalloproteinases, plasminogen-activators and their inhibitors in the synovial fluids of patients with rheumatoid arthritis during chemical synoviorthesis, Clin. Chim. Acta., 244*, 17-33 (**1996**).

[25] O'Byrne, E. M., Parker, D. T., Roberts, E. D., Goldberg, R. L., MacPherson, L. J., Blancuzzi, V., Wilson, D., Singh, H. N., Ludewig, R. and Ganu, V. S. *Oral administration of a matrix metalloproteinase inhibitor, CGS 27023A, protects the cartilage proteoglycan matrix in a partial meniscectomy model of osteoarthritis in rabbits, Inflamm. Res., 44*, S117-S118 (**1995**).

[26] Doughty, J. R., O'Byrne, E., Spirito, S., Blancuzzi, V., Singh, H. N. and Goldberg, R. L. *The effect of CGS 27023A on the level of 3B3 (-) epitope in a rabbit meniscectomy model, Inflamm. Res., 46*, S139-S140 (**1997**).

[27] Brewster, M., Lewis, E. J., Wilson, K. L., Greenham, A. K. and Bottomley, K. M. *Ro 32-3555, an orally active collagenase selective inhibitor, prevents structural damage in the STR/ORT mouse model of osteoarthritis, Arthritis Rheum., 41*, 1639-1644 (**1998**).

[28] Wojtowicz-Praga, S. M., Dickson, R. B. and Hawkins, M. *Matrix metalloproteinase inhibitors, Invest. New Drugs, 15*, 61-75 (**1997**).

[29] Bramhall, S. R. *The matrix metalloproteinases and their inhibitors in pancreatic cancer, Int. J. Pancreatol., 21*, 1-12 (**1997**).

[30] Brown, P. D. *Matrix metalloproteinase inhibitors in the treatment of cancer, Med. Oncol., 14*, 1-10 (**1997**).

[31] Yong, V. W., Krekoski, C. A., Forsyth, P. A., Bell, R. and Edwards, D. R. *Matrix metalloproteinases and diseases of the CNS, Trends Neurosci., 21*, 75-80 (**1998**).

[32] Matyszak, M. K. and Perry, V. H. *Delayed-type hypersensivity lesions in the*

central nervous system are prevented by inhibitors of matrix-metalloproteinases, J. Neuroimmunol., 69, 141-149 (**1996**).

[33] Coker, M. L., Thomas, C. V., Clair, M. J., Hendrick, J. W., Krombach, S. R., Galis, Z. S. and Spinale, F. G. *Myocardial matrix metalloproteinase activity and abundance with congestive heart failure, Am. J. Physiol., 274,* H1516-H1523 (**1998**).

[34] Spinale, F. G., Coker, M. L., Krombach, S. R., Mukherjee, R., Hallak, H., Houck, W. V., Clair, M. J., Kribbs, S. B., Johnson, L. L., Peterson, J. T. and Zile, M. R. *Matrix metalloproteinase inhibition during the development of congestive heart failure: effects on left ventricular dimensions and function, Circ. Res., 85,* 364-376 (**1999**).

[35] Tyagi, S. C. *Dynamic role of extracellular matrix metalloproteinases in heart failure, Cardiovasc. Pathol., 7,* 153-159 (**1998**).

[36] Burnett, D., Afford, S. C., Campbell, E.J., Rios-Mollineda, R. A., Buttle, D. J. and Stockley, R. A. *Evidence for lipid-associated serine proteases and metalloproteases in human bronchoalveolar lavage fluid, Clin. Sci., 75,* 601-607 (**1988**).

[37] Finlay, G. A., Russell, K. J, McMahon, K. J, D'Arcy, E. M, Masterson, J. B, FitzGerald, M. X. and O'Connor, C. M. *Elevated levels of matrix metalloproteinases in bronchoalveolar lavage fluid of emphysematous patients, Thorax, 52,* 502-506 (**1997**).

[38] Ohno, I., Ohtani, H, Nitta, Y., Suzuki, J., Hoshi, H., Honma, M., Isoyama, S., Tanno, Y., Tamura, G., Yamauchi, K., Nagura, H. and Shirato, K. *Eosinophils as a source of matrix metalloproteinase-9 in asthmatic airway inflammation, Am. J. Respir. Cell Mol. Biol., 16,* 212-219 (**1997**).

[39] Palmgren, M. S, deShazo, R. D. and Carter, R. M. *Mechanisms of neutrophil damage to human alveolar extracellular matrix: The role of serine and metalloproteases, J. Allergy Clin. Immunol., 4,* 905-915 (**1992**).

[40] Maskos, K. and Bode, W. *Structural basis of matrix metalloproteinases and tissue inhibtitors of metalloproteinase, Molecular biotechnology, 25,* 241-266 (**2003**).

[41] Van Wart, H. E. *In Handbook of Proteolytic Enzymes*, Barret, A. J., Rawlings, N. D., Woessner, J. F., Eds., Academic Press, Oxford, pp 368-71 (**1998**).

[42] Grams, F., Crimmin, M., Hinnes, L., Huxley, P., Pieper, M., Tschesche, H. and Bode, W. *Structure determination and analysis of human neutrophil collagenase complexed with a hydroxamate inhibitor, Biochemistry, 34*, 14012-14020 (**1995**).

[43] Supuran, C. T. and Scozzafava, A. *In Proteinase and Peptidase Inhibition: Recent Potential Targets for Drug Development*, Smith, H. J., Simons, C., Eds., Taylor and Francis: London And New York, pp 35-61 (**2002**).

[44] Lovejoy, B., Hassell, A. M., Luther, M. A., Weigl, D. and Jordan, S. R. *Crystal structures of recombinant 19-kDa human fibroblast collagenase complexed to itself, Biochemistry, 33*, 8207-8217 (**1994**).

[45] Birkedal-Hansen, H., Moore, W. G., Bodden, M. K., Windsor, L. J., Birkedal-Hansen, B., DeCarlo, A. and Engler, J. A. *Matrix metalloproteinases: A review, Crit. Rev. Oral. Biol. Med., 4*, 197-250 (**1993**).

[46] Graff von Roedern, E., Grams, F., Brandstetter, H. and Moroder, L. *Bis-substituted malonic acid hydroxamate derivatives as inhibitors of human neutrophil collagenase (MMP8), J. Med. Chem., 41*, 3041-3047 (**1998**).

[47] Brandstetter, H., Engh, R. A., Graf von Roedern, E., Moroder, L., Huber, R. and Bode, W. *Structure of malonic acid-based inhibitors bound to human neutrophil collagenase. A new binding mode explains apparently anomalous data, Protein Science, 7*, 1303-1309 (**1998**).

[48] Kiyama, R., Tamura, Y., Watanabe, F., Tsuzuki, H., Ohtani, M. and Yodo, M. *Homology modeling of gelatinase catalytic domains and docking simulations of novel sulfonamide inhibitors. J. Med. Chem., 42*, 1723-1738 (**1999**).

[49] Pavlovsky, A. G., Williams, M. G., Ye, Q. Z., Ortwine, D. F., White, A. D., Dhanaraj, V., Roth, B. D., Johnson, L. L., Hupe, D., Humblet, C. and Blundell, T. L. *X-ray structure of human stromelysin catalytic domain complexed with nonpeptide inhibitors: Implications for inhibitor selectivity, Protein Science, 8*, 1455-1462 (**1999**).

[50] Skotnicki, J. S., Digrandi, M. J. and Levin, J. I. *Design strategies for the identification of MMP-13 and TACE inhibitors, Curr. Opin. Drug Discov. Devel.,*

6, 742-759 (**2003**).

[51] Rudek, M. A., Venitz, J. and Figg, W. D. *Matrix metalloproteinase inhibitors: Do they have a place in anticancer therapy?*, *Pharmacotherapy*, *22*, 705-720 (**2002**).

[52] Mitchell, P. G., Magna, H. A., Reeves, L. M., Lopresti-Morow, L. L., Yocum, S. A., Rosner, P. J., Geoghegan K. F. and Hambor, J. E. *Cloning, expression, and type II collagenolytic activity of matrix metalloproteinase-13 from human osteoarthritic cartilage*, *J. Clin. Invest.*, *97*, 761-768 (**1996**).

[53] Lohmander, L. S., Neame, P. J. and Sandy, J. D. *The structure of aggrecan fragments in human synovial fluid: Evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis*, *Arthritis Rheum.*, *36*, 1214-1222 (**1993**).

[54] Foda, H. D., George, S., Conner, C., Drews, M., Tompkins, D. C. and Zucker, S. *Activation of human umbilical vein endothelial cell progelatinase A by phorbol myristate acetate: a protein kinase C-dependent mechanism involving a membrane-type matrix metalloproteinase*, *Lab. Invest.*, *74*, 538-545 (**1996**).

[55] Newell, K. J., Witty, J. P., Rodgers, W. H. and Matrisian, L. M. *Expression and localization of matrix-degrading metalloproteinases during colorectal tumorigenesis*, *Molec. Carcinogenesis*, *10*, 199-206 (**1994**).

[56] Sternlicht, M. D., Bissell, M. J. and Werb, Z. *The matrix metalloproteinase stromelysin-1 acts as a natural mammary tumor promoter*, *Oncogene*, *19*, 1102-1113 (**2000**).

[57] Yip, D., Ahmad, A., Karapetis, C. S., Hawkins, C. A. and Harper, P. G. *Matrix metalloproteinase inhibitors: Applications in oncology*, *Invest. New Drugs*, *17*, 387-399 (**1999**).

[58] Nelson, A. R., Fingleton, B., Rothenberg, M. L. and Matrisian, L. M. *Matrix metalloproteinases: Biologic activity and clinical implications*, *J. Clin. Oncol.*, *18*, 1135-1149 (**2000**).

[59] Maskos, K., Fernandez-Catalan, C., Huber, R., Bourenkov, G. P., Bartunik, H., Ellestad, G. A., Reddy, P., Wolfson, M. F., Rauch, C. T., Castner, B. J., Davis, R., Clarke, H. R. G., Petersen, M., Fitzner, J. N., Cerretti, D. P., March, C. J., Paxton,

R. J., Black, R. A. and Bode, W. *Crystal structure of the catalytic domain of human tumor necrosis factor-alpha-converting enzyme, Proc. Natl. Acad. Sci. U.S.A., 95*, 3408-3412 (**1998**).

[60] Newton, R. C. and Decicco, C. P. *Therapeutic potential and strategies for inhibiting tumor necrosis factor-alpha, J. Med. Chem., 42*, 2295-2314 (**1999**).

[61] Black, R. A. and White, J. M. *ADAMs: Focus on the protease domain, Curr. Opin. Cell Biol., 10*, 654-659 (**1998**).

[62] Moss, M. L., White, J. M., Lambert, M. H. and Andrews, R, C. *TACE and other ADAM proteases as targets for drug discovery, Drug Discov. Today, 6*, 417-426 (**2001**).

[63] Feldmann, M. and Maini, R. N. *Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned?, Annu. Rev. Immunol., 19*, 163-196 (**2001**).

[64] Van Assche, G. and Rutgeerts, P. *Anti-TNF agents in Crohn's disease, Expert Opin. Invest. Drugs, 9*, 103-111 (**2000**).

[65] Kristensen, M., Chu, C. Q., Eedy, D. J., Feldmann, M., Brennan, F. M. and Breathnach, S. M. *Localization of tumour necrosis factor-alpha (TNF-alpha) and its receptors in normal and psoriatic skin: epidermal cells express the 55-kD but not the 75-kD TNF receptor, Clin. Exp. Immunol., 94*, 354-362 (**1993**).

[66] Shakoor, N., Michalska, M., Harris, C. A. and Block, J. A. *Drug-induced systemic lupus erythematosus associated with etanercept therapy, Lancet, 359*, 579-580 (**2002**).

[67] Rawling, N. D. and Barret, A. J. *Evolutionary families of metallopeptidases, Methods Enzymol., 248*, 183-228 (**1995**).

[68] Bond, M. D. and Van Wart, H. E. *Purification and separation of individual collagenases of Clostridium histolyticum using red dye ligand chromatography, Biochemistry, 23*, 3077-3085 (**1984**).

[69] Bond, M. D. and Van Wart, H. E. *Characterization of the individual collagenases from Clostridium histolyticum, Biochemistry, 23*, 3085-3091 (**1984**).

[70] Van Wart, H. E. and Stienbrink, D. R. *A continuous spectrophotometric assay for Clostridium histolyticum collagenases, Anal. Biochem., 113*, 356-365 (**1981**).

[71] Matsushita, O., Jung, C. M., Minami, J., Katayama, S., Nishi, N. and Okabe, A. *A*

study of the collagen-binding domain of a 116-kDa Clostridium histolyticum collagenases, J. Biol. Chem., 273, 3643-3648 (**1998**).

[72] Jung, C. M., Matsushita, O., Katayama, S., Minami, J., Sakurai, J. and Okabe, A. J. *Identification of metal ligands in the Clostridium histolyticum collagenases, J. Bacteriol., 181*, 2816-2822 (**1999**).

[73] Schiff, W. M., Speaker, M. G. and McCormick, S. A. *The collagen shield as a collagenase inhibitor and clinical indicator of collagenase activity on the ocular surface, CLAO J., 18*, 59-63 (**1992**).

[74] Groos, E. B. *In cornea: Fundamentals of cornea and external disease*, Krachmer, J. H., Mannis, M. J., Holland, E. J Eds., Mosby-Year Book, St. Louis, MO, Vol.6, pp 105-142 (**1997**).

[75] Rood, J. I. *Virulence genes of Clostridium perfringens, Annu. Rev. Microbiol., 52*, 333-360 (**1998**).

[76] Matsushita, O., Jung, C. M., Minami, J., Katayama, S., Minami, J., Takashi, Y. and Okabe, A. *Gene duplication and multiplicity of collagenases in Clostridium histolyticum, J. Bacteriol., 181*, 923-933 (**1999**).

[77] Hansch, C., Maloney, P. P., Fujita, T. and Muir, R.M. *Correlation of biological activity of phenoxyacetic acids with Hammett substituent constants and partition coefficients, Nature, 194*, 178-180 (**1962**).

[78] Hansch, C. and Leo, A. *Exploring QSAR: Fundamentals and applications in chemistry and biology*, American Chemical Society, Washington, D.C (**1995**).

[79] Hansch, C. and Klein, T. *Molecular graphics and QSAR in the study of enzyme-ligand interactions. On the definition of bioreceptors, Acc. Chem. Res., 19*, 392-400 (**1986**).

[80] Blaney, J. M. and Hansch, C. *Application of molecular graphics to the analysis of macromolecular structures*, Comprehensive Medicinal Chemistry, Vol. 4, Pergamon Press, pp 230-287 (**1990**).

[81] Blaney, J. M., Hansch, C., Silipo, C. and Vittoria, A. *Structure-activity relationships of dihydrofolate reductase inhibitors, Chem. Rev. 84*, 333-407 (**1984**).

[82] Hansch, C. and Blaney, J. M. *In, drug design: Fact or fantasy?*, G. Jolles and

Wooldridge, Eds., Academic Press, pp. 185-208 (**1984**).

[83] Hansch, C. and Klein, T. *Quantitative structure-activity relationships and molecular graphics in evaluation of enzyme-ligand interactions, Methods Enzymol., 202*, 512-543 (**1991**).

[84] Carrieri, A., Altomare, C., Barreca, M. L., Contento, A., Carotti, A. and Hansch, C. *Papain catalyzed hydrolysis of aryl esters: A comparison of the Hansch, docking, and CoMFA methods, Il Farmaco, 49*, 573-585 (**1994**).

[85] Selassie, C. D. and Klein, T. E. *In: 3-D QSAR and drug design theory methods and applications*, H. Kubinyi, Ed., ESCOM Publishers, Leiden, pp. 257-280 (**1993**).

[86] Hansch, C. A *Quantitative approach to biochemical structure-activity relationships, Acc. Chem. Res., 2*, 232-239 (**1969**).

[87] Hansch, C. and Fujita, T. *ρ-σ-π Analysis. A method for the correlation of biological activity and chemical structure, J. Amer. Chem. Soc., 86*, 1616-1626 (**1964**).

[88] Hansch, C. In: *Drug Design*, Ed. Arien's E.J. vol. 1, Academic Press, New York, pp. 281-332 (**1971**).

[89] Free, S. M. Jr. and Wilson, J. W. *A mathematical contribution to structure-activity studies, J. Med. Chem., 7*, 395-399 (**1964**).

[90] Fujita, T. and Ban, T. *Structure-activity study of phenethylamines as substrates of biosynthetic enzymes of sympathetic transmitters, J. Med. Chem., 14*, 148-152 (**1971**).

[91] Martin, Y. C., Holland, J. B., Jaorbe, C. H. and Plotnikoff, N. *Discriminant analysis of the relationship between physical properties and the inhibition of monoamine oxidase by aminotetralins and aminoindans, J. Med. Chem., 4*:409-413 (**1974**).

[92] Kowalski, B. R. and Bender, C. F. *The application of pattern recognition to screening prospective anticancer drugs: Adenocarcinoma 755 biological activity test, J. Am. Chem. Soc., 3*, 916-918 (**1974**).

[93] Chu, K C. *Applications of artificial intelligence to chemistry: Use of pattern recognition and cluster analysis to determine the pharmacological activity of*

some organic compounds, Analyt. Chem., 46, 1181-1187 **(1974)**.

[94] Levitan, H. and Berker, J. L. *Membrane permeability: Cation selectivity reversibly altered by salicylate, Science, 176,* 63-64 **(1972)**.

[95] Leo, A., Hansch, C. and Elkins, D. *Partition coefficients and their uses, Chem. Rev., 71,* 525-616 **(1971)**.

[96] Hammet, L. P. *Physical Organic Chemistry,* McGraw Hill, New York **(1940)**.

[97] Taft, R.W. *In: Steric Effects in Organic Chemistry,* Ed. Newman, M.S., Wiley, New York, pp. 556-580 **(1956)**.

[98] Hansch, C., Leo, A., Unger, S.H., Kim, K. H., Nikaitani, D. and Lein, E. J. *Aromatic substituent constants for structure-activity correlations, J. Med. Chem., 16,* 1207-1216 **(1973)**.

[99] Dunn III, W. J. and C. Hansch, C. *Chemicobiological interactions and the use of partition coefficients in their correlation, Chem.-Biol. Inter. 9,* 75-95 **(1974)**.

[100] Moriguchi, I. and Kanada, Y. *Use of van der Waals volume in structure-activity studies, Chem. Pharm. Bull., 25,* 926-935 **(1977)**.

[101] Gupta, S. P., Bhatnagar, R. P., Singh, P. and Bindal, M. C. *The relationship of cellular respiration inhibition activity of 7-substituted 4-hydroxyquinoline-3-carboxylic acids with van der waals volume, Res. Comm. Chem. Path. Pharmacol., 25,* 111-119 **(1979)**.

[102] Bindal, M. C., Singh, P., Bhatnagar, R. P. and Gupta, S. P. *The relationship of vasodilator activity of adenosine analogues with molecular connectivity and van der waals volume, Arzneim. Forsch., 30,* 924-928 **(1980)**.

[103] Kumar, K., Bindal, M. C., Singh, P. and Gupta, S. P. *Effect of molecular size on carbonic anhydrate inhibition by sulfonamides, Int. J. Quant. Chem., 20,* 123-129 **(1981)**.

[104] Gupta, S. P., Singh, P. and Bindal, M. C. *Structure-activity studies on LSD analogs using van der waals volume, Eur. J. Med. Chem., 16,* 446-448 **(1981)**.

[105] Gupta, S. P., Singh, P. and Bindal, M. C. *Effect of molecular size on inhibition of synaptosome dopamine uptake by antihistaminic pheniramines, Indian J. Biochem. Biophys., 19,* 143-144 **(1982)**.

[106] Handa, A., Bindal, M. C., Prabhakar, Y. S. and Gupta, S. P. *Dependance of*

anesthetic activity on molecular polarizibility and van der waals volume, Indian J. Biochem. Biophys., 20, 318-320 (**1983**).

[107] Verloop, A., Hoogenstraaten, W. and Tifter, J. *In: Drug Design,* vol. 7, Ed. Arien's E.J., Academic Press, New York, pp. 165-193 (**1976**).

[108] Gupta, S. P., Prabhakar, Y. S. and Handa, A. *QSAR studies on 4-hydroxyguinoline-3-carboxylic acids as inhibitors of cell respiration using molecular connectivity and van dar waals volume, Res. Commun. Chem., Pathol. Pharmacol., 42,* 455-562 (**1983**).

[109] Gupta, S. P., Prabhakar, Y. S., Handa, A. and Bindal, M.C. *A quantitative analysis of dependence of ribonucleoside diphosphate reductase inhibitory activity of thiosemicarbazones on molecular size, Arzneim. Forsch., 34,* 147-150 (**1984**).

[110] Kier, L. B. and Hall, L. H. *Molecular connectivity in chemistry and drug research,* Academic Press, New York (**1976**).

[111] Macfarland, J. W. *On the parabolic relationship between drug potency and hydrophobicity, J. Med. Chem., 13*:1192-1196 (**1970**).

[112] Penniston, I. T., Beckett, L., Bentley, D. L. and Hansch, C. *Passive permeation of organic compounds through biological tissue: A non-steady-state theory, Mol. Pharmacol., 5,* 333-341 (**1969**).

[113] Hansch, C., Steward, A. R., Iwasa, J. and Deutsch, E. W. *The use of a hydrophobic bonding constant for structure-activity correlations, Mol. Pharmacol., 1,* 205-213 (**1965**).

[114] Hyde, R. M. *Relationships between the biological and physicochemical properties of series of compounds, J. Med. Chem., 18,* 231-233 (**1975**).

[115] Franke, R. and Schmidt, W. *Parabolic relationship between biological activity and hydrophobicity in congenergic series: transport or protein binding?, Acta. Biol. Med. Ger., 31,* 273-287 (**1973**).

[116] Yalkowsky, S. H. and Flynn, G. L. *Transport of alkyl homologs across synthetic and biological membranes: A new model for chain length-activity relationships, J. Pharm. Sci., 62,* 210-217 (**1973**).

[117] Kubinyi, H. *Quantitative structure-activity relationships. IV. Non-linear*

dependence of biological activity on hydrophobic character: A new model, Arzneim. Forsch., 26, 1991-1997 (**1976**).

[118] Kubinyi, H. *Lipophilicity and drug activity, Prog. Drug Res., 23,* 97-198 (**1979**).

[119] Kubinyi, H. *Lipophilicity and biological activity: Drug transport and drug distribution in model systems and in biological systems, Arzneim. Forsch., 29,* 1067-1080 (**1979**).

[120] Seydel, J.K. In: *Strategy in Drug Research,* Ed. Buisman, J.A.K (Ed.), Elsevier, Amsterdam, pp. 179-202 (**1982**).

[121] Seydel, J. K. and Schaper, K. J. *Quantitative structure-pharmacokinetic relationships and drug design, Pharmacol. Ther., 15,* 131-182 (**1981**).

[122] Kubinyi, H. *Quantitative structure-activity relationships. 7. The bilinear model, a new model for nonlinear dependence of biological activity on hydrophobic character, J. Med. Chem., 20,* 625 (**1977**).

[123] Li, R. L., Hansch, C., Mathews, D., Blaney, J. M., Langridge, R., Delcamp, T. J., Susten, S. S. and Freisheim, J. H. *A comparison by QSAR, crystallography and computer graphics of the inhibition of various dihydrofolate reductases by 5-(x-benzyl)-2,4-diamino pyrimidines, Quant. Struct-Act. Relat., 1,* 1-7 (**1982**).

[124] Kubinyi, H. In: QSAR *in Design of Bioactive Compounds,* Ed. Kuchar, M., J.R Prous Science, Barcelona, Spain, pp. 321-368 (**1984**).

[125] Martin, Y. C. *A practitioner's perspective of the role of quantitative structure-activity analysis in medicinal chemistry, J. Med. Chem., 24,* 229-237, (**1981**).

[126] Hansch. C. *The use of substituent constants in drug modification, Farmaco, 23,* 293-320 (**1968**).

[127] Martin, Y. C. In: *Quantitative Drug Design,* Marcel Dekker, New York, (**1978**).

[128] McCammon, J. A., Gelin, B. R., Karplus, M. and Wolynes, P. G. *The hinge-bending mode in lysozyme, Nature, 262,* 325-326 (**1976**).

[129] McCammon, J. A., Gelin, B. R., Karplus, M. and Wolynes, P. G. *Dynamics of folded proteins, Nature, 267,* 585-590 (**1977**).

[130] McCammon, J. A. and Karplus, M. *Internal motions of antibody molecules, Nature, 268,* 765-766 (**1977**).

[131] Hallenga, K. and Koenig, S. H. *Protein rotational relaxation as studied by*

solvent 1H and 2H magnetic relaxation, Biochemistry, **15**, 4255-4264 (**1976**).

[132] Baldwin, R.L. *Intermediates in protein folding reactions and the mechanism of protein folding, Annu. Rev. Biochem.*, *44*, 453-475 (**1975**).

[133] Hansch, C. and Calef, D. E. *Structure-activity relationships in papain-ligand interactions, J. Org. Chem.*, *41*, 1240-1243 (**1976**).

[134] Hansch, C. and Leo, A. J. *Substituent constants for correlation analysis in chemistry and biology*, John Wiley, New York (**1979**).

CHAPTER 2

PARAMETERS USED
AND
THEIR CALCULATIONS

2 PARAMETERS USED AND THEIR CALCULATIONS

This chapter discusses the methodology of calculation of various distinct parameters, on which most of the biological activities are found to depend and which are useful in QSAR studies.

2.1 Hydrophobic Parameter [log P]

The fragment method suggested by Hansch and Leo [1] for calculating logP, where P is the partition coefficient of the solute in octanol-water system, is known as constructionist approach or synthetic approach. Experimentally determined logP values can often be reproduced or approached theoretically with the help of this approach. The basic assumption of this approach is: the logP of a solute can be expressed as a linear sum of fundamental structural constants known as fragments (*f*) and factors (*F*) that affect the partitioning equilibrium.

$$\log P = \sum_{1}^{n} a_n f_n + \sum_{1}^{m} b_m F_m \qquad (2.1)$$

Carefully conducted partitioning experiment and statistical survey of the then available partition data have been used in assigning values to the fragments and factors. The working principle is summarized in the following paragraphs.

In this approach carbon atoms are divided into two categories: isolating carbons (IC) and nonisolating carbons (NIC). Isolating carbons are those having either four single bonds (at least two of which are to nonheteroatoms) or else are multiply-bonded to other carbon atoms.

Nonisolating carbons atoms are carbon atoms multiply-bonded to hetero atoms. For example –C= in CH_2=CH_2 is an IC but not in H_2C=O. Fragments are of two types: (i) fundamental fragments defined as fragments whose free valency will lead to isolating carbons; (i) derived fragments, a derivative of fundamental fragments (e.g. CF_3). A

fundamental fragment can be either a single atom or a group of multiple atoms (e.g. –C=O, -C=N, etc.). A single atom fundamental fragment can be either an isolating carbon atom or a hydrogen or a heteroatom all of which are bonded to ICs. Depending on its nature a fragment will come under one of the following classes:

(i) **Non-polar fragments:** These are simple ICs and hydrogens attached to ICs.

(ii) **H-polar fragments:** A fragment that can be expected to form H-bonds either by accepting or donating an electron pair (e. g. –OH, -COOH, $-NH_2$ etc.).

(iii) **S-polar fragments:** A fragment that is strongly electron withdrawing with little tendency to form H-bonds (e.g. halogens). In expressing fragments, the structural formulae (WLN code) of the respective fragments will be written as subscripts of "*f*" for example as *f*-NH-CO-NH- present in $CH_3NHCONHCH_3$. Various factors (F) are designed to account for the intramolecular forces and factors that affect the partitioning equilibrium of the solute. All these F_s are identified with the help of different subscripts and superscripts. The superscripts are mentioned in the factor table (Table (2.2)). The superscripts are applicable also to fragments.

They are listed as:

1. None = aliphatic structural attachment
2. ϕ = attachment to aromatic ring; if bivalent the attachment is from left as written
3. $1/\phi$ = as 2 but attachment from right as written
4. $\phi\phi$= two aromatic attachments
5. X = aromatic attachment, value enhanced by second, electron-withdrawing substituents ($\sigma_I \geq \pm 0.35$) and
6. IR = benzyl attachment

Underlining any symbol means it is present in a ring system. Whenever halogens and H-polar fragment are separated by only one IC an additional factor will come into operation.

In calculating the logP of any compound, the first step is dividing that compound into "well defined" fragments based on above discussion and then searching for different factors operating in between the fragments within the structure of the molecule. Now the sum of all these fragments and factors will give the calculated logP of that compound. It is always safe to break any compound, especially compound containing hetero atoms, into fundamental fragments rather than into derived fragments. Some important fragments values and factor values are listed in Tables (2.1) and (2.2), respectively. A simple example for logP calculation is shown below:

Example, Toluene ($C_6H_5CH_3$): This can be treated as a compound comprising six aromatic carbons, one aliphatic carbon and eight hydrogens. The fragments can be expressed as:

$6f^{a}C + f_C + 8f_H = \text{logP (Toluene)}$

$6(0.13) + 0.20 + 8(0.23) = 2.82$ (calcd.), 2.80 (obsd.)

Since aromatic ring is excluded from bond factor there is no F_b term in the above equation. And here aliphatic chain length is one (-CH3), so (n-1) F_b is equal to zero (C-H bonds are excluded from factors). The logP of this compound can also be calculated from derived fragments as:

$f^{a}C_6H_5 + fCH_3 = \text{logP (Toluene)}$

$1.9 + 0.89 = 2.79$ (calcd.)

Sometimes calculated logP values of compounds deviate very much from the experimentally determined values. For example, observed logP of 1,2-methylenedioxybenzene is 2.08, but the calculated values comes out to be 1.34 only. This large difference may be due to factors beyond the control of this method. However, since it is an additive model, it will serve the purpose of drug design when used in a congeneric series of compounds. Further details are given in the literature[1].

Table 2.1. Some common fragment constants[a]

Without Carbon	f	f^{ϕ}	$f^{\phi\phi}$	With Carbon	f	f^{ϕ}	$f^{\phi\phi}$
-Br	0.20	1.09		C	0.20	0.20	
-Cl	0.06	0.94		$-CF_3$[b]		1.11	
-F	-0.38	0.37		-CN	-1.27	0.34	
-I	0.59	1.35		-CON	-3.04	-2.80	-1.93
-N	-2.18	-0.93	-1.13	-C(O)-	-1.90	-1.09	-0.50
$-NO_2$	-1.16	-0.03		$-CO_2-$	-1.49	-0.56	-0.09
-O-	-1.82[c]	-0.61	0.53	$-CO_2-$	-5.19	-4.13	
-H	0.23	0.23		-COH	-1.10	-0.42	
-NH-	-2.15	-1.03	-0.09	$-CO_2H$	-1.11	-0.03	
$-NH_2$	-1.54	-1.00		$-CONH_2$	-2.18	-1.26	
-OH	-1.64	-0.44		-CONH-	-2.71	-1.81	-1.06
-SH	-0.23	0.62		-NHCONH-	-2.18	-1.57	-0.82

Fused in Aromatic Ring

Without Carbon	f^{ϕ}	Without Carbon	f^{ϕ}	With Carbon	f^{ϕ}	With Carbon	f^{ϕ}
-N=	-1.12	-N=N-	-2.14	<u>C</u>	0.13	-CH-	0.35
-N	-1.60	-O-	-0.08	<u>C</u>	0.25[d]	-C(O)-	-0.59
$-N^{\phi}$	-0.56	-NH-	-0.65	<u>C</u>[a]	0.44[e]	-OC(O)-	-1.40

[a]Taken from ref. [1], [b]Derived fragment, [c]For methyl esters and ethylene oxide, use - 1.54, [d]For ring fusion carbon, [e]For ring fusion–hetero.

Table (2.2): List of some factors[a]

	Involving Bonds			
	Unsaturation Double	Triple	Proportional to Length: x(n-1)	Geometric Short Chains: 1-time
Normal	F (=) = -0.55	F(≡) = -1.42	Chain: F_b = -0.12	Alkane Chain: F_{cBr} = 0.13
Conjugate to φ	F^{φ} (=) = -0.42		Ring[b]: F_b = -0.09	H-Polar Fragment: F_{gBr} = -0.22
Conjugate to 2φ	$F^{\varphi\varphi}$ (=) = 0.0	$F^{\varphi\varphi}$ (≡) = 0.0	Branching: F_{bYN} = -0.20[c] F_{bYP} = -0.20[d]	Ring Cluster: F_{rCl} = -0.45
	Involving Multiple Halogenation[e]			
	On same Carbon (germinal) F_{mhCm}		(n=2) = 0.30 (n=3) = 0.53 (n=4) = 0.72	On adjacent Carbon (vicinal) F_{mhVn} : 0.28(n-1)
	Involving H-polar Proximity			
Chain	$F_p^1 = -0.42\ \Sigma f_1 + f_2$ $F_p^2 = -0.26\ \Sigma f_1 + f_2$ $F_p^3 = -0.10\ \Sigma f_1 + f_2$		Aliphatic: $F_p^1 = -0.32\ \Sigma f_1 + f_2$ Ring: $F_p^2 = -0.20\ \Sigma f_1 + f_2$	Aromatic: $F^{\varphi}{}_p^1 = -0.16\ \Sigma f_1 + f_2$ $F^{\varphi}{}_p^2 = -0.08\ \Sigma f_1 + f_2$
	Involving Intramolecular H-bond			
	F_{HBN} = 0.60 for Nitrogen			F_{HBO} = 1.0 for Oxygen

[a]Taken from ref. [1]
[b]Aromatic rings are excluded
[c]For amine
[d]For phosphorous ester
[e]Value per halogen atom

2.2 Hydrophobic Constant (π) of Substituents

Although logP can be used as measure of the hydrophobicity of a whole molecule, one often works with a set of derivatives of a parent compound in which a large portion of the structure remains constant. In such a case, knowing the relative hydrophobicity of substituents can be sufficient for correlation analysis. Sometimes it has been found that only substituents in certain positions interact hydrophobically with a given biosystem [2,3]. To enable one to work with the relative hydrophobicity character from electronic and steric effects of substituents, the parameter π has been defined analogous to σ as

$$\pi_X = \log P_X - \log P_H \qquad (2.2)$$

In this expression, P_X is the partition coefficient of a derivative and P_H that of the parent compound, for example:

$$\pi_{Cl} = \log P_{C6H5Cl} - \log P_{C6H6} \qquad (2.3)$$
$$0.71 = 2.84 - 2.13$$

A positive value for π means that relative to H the substituents favors the octanol phase. A negative value indicates its hydrophilic character relative to H. The value of π varies somewhat from system to system. Certain π value are given in Table (2.3).

2.3 Electronic Parameter (σ)

The development of electronic parameter is one of the most important breakthrough for mechanistic organic chemistry which came in 1935 when L.P. Hammett [4] proposed the following equation to define an electronic parameter σ.

$$\sigma = \log K_X - \log K_H \qquad (2.4)$$

In equation (2.4), K_H is the ionization constant of benzoic acid in water at 25°C and K_X is the ionization constant for meta or para derivatives under the same experimental conditions. Positive values of σ represent the electron-withdrawing and the negative ones electron-donating character of substituents in the aromatic ring. For certain substituents, σ values are given in Table (2.3).

2.4 Molar Refractivity (MR)

In various organic reactions, dispersion forces play an important role and these could be modeled by the molar refractivity (MR) of substituents. Experimentally, MR is usually obtained via the Lorentz-Lorentz equation.

$$MR = \frac{n^2 - 1}{n^2 + 2} \cdot \frac{MW}{d} \qquad (2.5)$$

where n is the index of refraction, d is the density, and MW is the molecular weight of a compound. Since MR is an additive constituent property of molecules, fragment values have been calculated for many common groups of atoms. It has generally been assumed that a positive coefficient with an MR term in a correlation equation suggests a binding action via dispersion forces. Such binding could produce a concomitant conformational change in a macromolecular binding site. If the conformational change favored the process under study, one would certainly expect a positive coefficient only with the MR term, however, if the conformational change were detrimental, a negative coefficient could result for the MR term [5]. Negative coefficient with MR have also been assumed to reflect steric hindrance of one kind or another. Some MR values used are tabulated in Table (2.3).

Table 2.3. Data on physicochemical parameters for some important substituents[a]

No	Substituent	π	σ_m	σ_p	MR
1	H	0.00	0.00	0.00	1.03
2	CH_3	0.56	-0.07	-0.17	5.65
3	C_2H_5	1.02	-0.07	-0.15	10.30
4	C_3H_7	1.05	-0.07	-0.13	14.96
5	i-C_3H_7	1.53	-0.07	-0.15	14.96
6	n-C_4H_9	2.13	-0.08	-0.16	19.61
7	F	0.14	0.34	0.06	0.92
8	Cl	0.71	0.37	0.23	6.03
9	Br	0.86	0.39	0.23	8.88
10	I	1.12	0.35	0.18	13.94
11	OCH_3	-0.02	0.12	-0.27	7.87
12	NH_2	-1.23	-0.16	-0.66	5.42
13	OH	-0.67	0.12	-0.37	2.85
14	COOH	0.32	0.37	0.45	6.93
15	$COOCH_3$	0.01	0.37	0.45	12.87
16	CF_3	0.88	0.43	0.54	5.02
17	NO_2	-0.28	0.71	0.78	7.36
18	CHO	-0.65	0.35	0.42	6.88
19	C_5H_5	1.96	0.06	-0.01	25.36
20	CN	-0.57	0.56	0.66	6.33
21	N_3	0.46	0.27	0.15	10.20
22	NHOH	-1.34	-0.04	-0.34	7.22
23	$CH{=}CH_2$	0.82	0.05	-0.02	10.99
24	$COCH_3$	-0.55	0.38	0.50	11.18
25	$COOC_2H_5$	0.51	0.37	0.45	17.47
26	$COOC_3H_7$	1.07	0.37	0.45	22.17
27	CH_2OH	-1.03	0.00	0.00	7.19
28	$CHOHCH_3$	-0.86	0.00	-0.07	11.82

Contd....

29	CH_2OCH_3	-0.78	0.02	0.03	12.07
30	SCH_3	0.61	0.15	0.00	13.82
31	NHCHO	-0.98	0.19	0.00	10.31
32	$OCOCH_3$	-0.64	0.39	0.31	12.47
33	$OCH(CH_3)_2$	0.85	0.10	-0.45	17.06
34	OC_3H_7	1.05	0.10	-0.25	17.06
35	$N(CH_3)_2$	0.18	-0.15	-0.83	15.55

[a]Taken fron ref. [13].

2.5 Polarizability (α)

The polarizability (abbreviated as Pol) of a molecule is a measure of the overall electronic charge distribution that can be distorted by an electric field. Molar refractivity (MR) has a strong correlation with molecular polarizability and is calculated by the Lorentz-Lorentz equation (2.5). It is related to polarizability as follows [5].

$$MR = \frac{4\pi N\alpha}{3} \qquad (2.6)$$

Where N is the Avogadro's number, α is the polarizability, $\pi = 3.14$. In molecules with large number of atoms the polarizability will be larger compared to smaller molecules. The polarizability of a molecule increases with both increasing size and increasing numbers of atoms in the molecule.

2.6 van der Waals Volume (V_w)

The van der Waals volume (V_w) has been found to be one of the most fundamental characteristic of the drug structure controlling biological activity. This determines the molecular size and shape of the compounds which are very important in aspect of drug-receptor interactions.

The values of the van der Waals radii used and calculated volume of atoms are listed in Table (2.4). Since van der Waals radii are grater than covalent radii, a correlation for sphere overlapping due to covalent bonding between atoms is needed for calculation of V_w of polyatomic molecules. The covalent bond lengths and correction values are tabulated in Table (2.5). A correlation for branching in the molecule is also included in the V_w calculation. Such correlation is also mentioned in the Table (2.5). All these values have been taken from literature [6].

Table 2.4. van der Waals radius and volume of atoms[a]

Atom		Radius (Å)	Sphere Volume (10^2Å^3)
C		1.7	0.206
H		1.1	0.056
N		1.5	0.141
O		1.4	0.115
S		1.8	0.244
F		1.4	0.115
Cl	alipahtic	1.7	0.206
	aromatic	1.8	0.244
Br	alipahtic	1.8	0.244
	aromatic	1.9	0.287
I	alipahtic	2.0	0.335
	aromatic	2.1	0.388
B		2.1	0.388
He		1.2	0.072
Ne		1.6	0.171
Ar		1.9	0.287
Kr		2.0	0.335
Xe		2.2	0.446

[a]Taken from ref. [6].

Table 2.5. Correction values of van der Waals volume, for sphere overlapping due to covalent bonding and branching[a]

Bond		Bond length (Å)	Correction value (10^2Å^3)
C-C		1.5	-0.078
C-H		1.1	-0.043
C-N		1.4	-0.060
C-O		1.4	-0.056
C-S		1.8	-0.066
C-F		1.4	-0.056
C-Cl	(aliphatic)	1.8	-0.058
C-Cl	(aromatic)	1.8	-0.066
C-Br	(aliphatic)	1.9	-0.060
C-Br	(aromatic)	1.9	-0.068
C-I	(aliphatic)	2.1	-0.063
C-I	(aromatic)	2.1	-0.072
C-B		1.6	-0.113
H-H		0.7	-0.030
N-H		1.0	-0.038
N-N		1.4	-0.050
N-O		1.4	-0.042
N-S		1.6	-0.061
O-H		1.0	-0.034
O-B		1.5	-0.079
S-H		1.3	-0.040
S-S		2.0	-0.062
S-F		1.6	-0.052
C=C		1.3	-0.094
C=N		1.3	-0.072
C=O		1.2	-0.068
C=S		1.6	-0.081

Contd....

N=N	1.2	-0.061
N=O	1.2	-0.053
S=O	1.5	-0.057
C≡C	1.2	-0.101
C≡N	1.2	-0.079
C≡C (aromatic)	1.4	-0.086
Branching for saturated Bond except bonding with H		-0.050

[a]Taken from ref. [6]

2.7 Molar Volume (MV)

The Molar volume (abbreviated as MV) of the molecule is a measure of overall bulk volume of the molecule. It calculated from the ratio of molecular weight (M.Wt) to the density (d) of the compounds [5].

$$MV = \frac{M.Wt}{d} \qquad (2.7)$$

2.8 Molecular Connectivity Index (χ)

Kier and Hall [7] introduced this additive topological parameter to drug design. Here the molecular connectivity index, χ, signifies the degree of branching or connectivity in a molecule.

Different version of χ are calculated from the hydrogen-suppressed graph of the molecule. For this purpose the hydrogen-suppressed graph will be decomposed, depending on the χ considered, into uniform parts called as subgraph(s). Here two types of connectivity indices, simple molecular connectivity index ($^{m}\chi$) and valence molecular connectivity index ($^{m}\chi^{v}$) are discussed. The superscript m is known as order of the connectivity index and is numerically equal to the number of non hydrogenic sigma bonds present in the subgraph of the particular χ.

A simple version of simple molecular connectivity index is first-order molecular connectivity index $^{1}\chi$, and it is computed by

$$^{1}\chi = \Sigma C_{ij} = \Sigma(\delta_i\,\delta_j)^{-1/2} \qquad (2.8)$$

where the summation extends to all connections or edges (C_{ij}) of the hydrogen-suppressed graph and δ_i and δ_j are integers assigned to each atom indicating the number of atom adjacent or connected to atom i and j which are formally bonded. Here, in

deriving this index, only the number of non-hydrogenic adjacent atoms are considered but not the nature of the atoms and the unsaturation in the molecule.

The valence molecular connectivity index, in contrast to the simple molecular connectivity index, takes into account the nature of the atoms as well as the unsaturation present in the molecules. Here the connectivity term δ^v is defined as:

$$\delta^v = Z^v_i - N_H \qquad (2.9)$$

in which Z^v_i is the number of valence electrons present in atom i and N_H is the number of hydrogens attached to it. A simple version of valence molecular connectivity index is first-order valence molecular connectivity index, $^1\chi^v$, and is formulated as:

$$^1\chi^v = \Sigma C_{ij} = \Sigma(\delta_i\, \delta_j)^{-1/2} \qquad (2.10)$$

The application of equation (2.8) for atoms beyond the second row in the periodic table leads to the same δ^v value for each family member, for example, seven for each halogen. Consideration of valence electrons (Z^v_i) of atom i together with its atomic number (Z_i) and the number of hydrogen atoms (h_i) attached to that atom will give appropriate δ^v value for atoms beyond second row in the periodic table. The mathematical expression for this is:

$$\delta^v = (Z^v_i - h_i) / (Z_i - Z^v_i - 1) \qquad (2.11)$$

According to this equation $\delta_{Cl} = 0.78$ and $\delta_{Br} = 0.26$. The δ^v value for some heteroatoms including halogens are listed in Table (2.6).

Only the above discussed connectivity indices are used in our studies. Higher order connectivity indices are discussed by Kier and Hall in their monograph [7].

Table 2.6. Valence delta (δ^v) values for heteroatoms[a]

Group	δ^v	Group	δ^v
NH_2	3	OH	5
NH	4	O	6
N	5	C=O	6
C≡N	5	Furan O	6
C=NH	4	O=NO	6
Pyridine N	5	H_2O	4
Nitro N	6	H_3O	3
NH_3	2	F	7
NH_4^+	1	Cl	0.78[b]
N^+	6	Br	0.26[b]
$=NH_2^+$	3	I	0.16[b]
		S	0.67[b]

[a]Taken from ref. [7], [b]Obtained from equation (2.11).

2.9 Electrotopological State Index (S)

The E-state index of an atom i (S_i) is calculated as follows [8]. To calculate S_i of an atom i, one first defines the intrinsic state I_i of an atom i as

$$I_i = (\delta_i^v + 1) / \delta_i \qquad (2.12)$$

where δ_i is the σ electron count of the atom i and δ_i^v is the valence vertex connectivity index of the same atom, which is calculated according to Eq. 2.11.

For higher quantum level atoms, intrinsic state is calculated as

$$I_i = [(2/N)^2\delta_i^v + 1] / \delta_i \qquad (2.13)$$

where N is the principal quantum number.

After calculating I_i, one calculates a factor ΔI_i for the atom i, using the equation,

$$\Delta I_i = \Sigma_{j=1} (I_i - I_j) / n^2 \qquad (2.14)$$

where n refers to the number of the atoms in the path i to j, including both i and j. I_i and ΔI_i are then used to find the E-state index S_i of the atom i according to the Eq:

$$S_i = I_i + \Delta I_i \qquad (2.15)$$

E-state index (S_i) of an atom is a measure of the availability of the π and lone pair electrons on the atom. The more electronegative atoms or groups have a richer content of π and lone pair electrons, giving rise to a higher calculated value of S_i.

2.10 Steric Parameter (E_s)

Steric effect of substitutents in organic reactions are very important. The first generally successful numerical definition of steric effects in organic reactions was proposed by Taft [9,10]. Following a suggestion of Ingold, Taft defined the steric constant E_s as:

$$E_s = \log (k_X/k_H)_A \qquad (2.16)$$

Where k refers to the rate constant for the acid hydrolysis (denoted by A) of esters of type $X\text{-}CH_2COOR$. The size of X will affect attainment of transition state, which is essential step for acid hydrolysis by water.

2.11 Verloop's Steric Parameters (L and B)

Verloop's steric parameters [11] L and B referring to length and breath of the substituents are calculated by a computer program called STERIMOL. There is only one length parameter, L, and five width parameters B_1-B_5. All are calculated from standard bond angles, bond lengths, van der Waals radii, and user-determined reasonable conformations. The width parameters are measured perpendicular to the bond axis and describe the positions, relative to the point of attachment and the bond axis, of five planes which closely surround the group. In contrast to E_s values which, because of the reaction on which they are based, cannot be determined for many substituents. Table (2.7) lists the Verloop's parameters for some important substituents.

For QSAR studies in this thesis, standard values for different parameters for various substituents have been taken from literature [12].

Table 2.7. Verloop's parameters for some important substituents[a]

No	Substituent	L (Å)	B_1 (Å)	B_2 (Å)	B_3 (Å)	B_4 (Å)
1	H	2.06	1.00	1.00	1.00	1.00
2	F	2.65	1.35	1.35	1.35	1.35
3	Cl	3.52	1.80	1.80	1.80	1.80
4	Br	3.83	1.95	1.95	1.95	1.95
5	I	4.23	2.15	2.15	2.15	2.15
6	CH_3	3.00	1.52	1.90	1.90	2.04
7	C_2H_5	4.11	1.52	1.90	1.90	2.97
8	n-C_3H_7	5.05	1.52	1.90	1.90	3.49
9	i-C_3H_7	4.11	2.04	2.76	3.16	3.16
10	c-C_3H_7	4.14	1.98	2.24	2.29	2.88
11	$CH_2C_6H_5$	3.63	1.52	3.11	3.11	6.02
12	CF_3	3.30	1.98	2.44	2.44	2.61
13	COOH	3.91	1.60	1.60	2.36	2.66
14	$COOCH_3$	4.85	1.90	1.90	2.36	3.36
15	$CONH_2$	4.06	1.60	1.60	2.42	3.07
16	CN	4.23	1.60	1.60	1.60	1.60
17	C_6H_5	6.28	1.70	1.70	3.11	3.11
18	p-ClC_6H_4	7.74	1.80	1.80	3.11	3.11
19	OH	2.74	1.35	1.35	1.35	1.93
20	OCH_3	3.98	1.35	1.90	1.90	2.87
21	OC_2H_5	4.92	1.35	1.90	1.90	3.36
22	$OCH_2C_6H_5$	8.20	1.35	3.03	3.11	3.11
23	NH_2	2.93	1.50	1.50	1.84	1.84
24	$NHCH_3$	3.53	1.50	1.90	1.90	3.08
25	NO_2	3.44	1.70	1.70	2.44	2.44

[a]Taken from ref. [13].

References

[1] Hansch, C. and Leo, A. J. *Substituent constants for correlation analysis in chemistry and biology*, John Wiley, New York (**1979**).

[2] Hansch, C., Deutsch, F. W. and Smith, R. N. *The use of substituent constants and regression analysis in the study of enzymatic reaction mechanisms, J. Am. Chem. Soc., 87*, 2738-2742 (**1965**).

[3] Yoshimoto, Y. and Hansch, C. *Correlation analysis of baker's studies on enzyme inhibition 2: Chymotrypsin, trypsin, thymidine phosphorylase, uridine phosphorylase, thymidylate synthetase, cytosine nucleoside deaminase, dihydrofolate reductase, malate dehydrogenase, glutamate dehydrogenase, lactate dehydrogenase, and glyceraldehyde-phosphate dehydrogenase, J. Med. Chem., 19*. 71-98 (**1976**).

[4] Hammet, L. P. *Some relations between reaction rates and equilibrium constants, Chem. Rev.*, 17, 125-136 (**1935**).

[5] Hansch, C. and Leo, A. *Exploring QSAR: Fundamentals and applications in chemistry and biology*, American Chemical Society, Washington, D.C (**1995**).

[6] Moriguchi, I. and Kanada, Y. *Use of van der Waals volume in structure-activity studies, Chem. Pharm. Bull., 25*, 926-935 (**1977**).

[7] Kier, L. B. and Hall, L. H. *Molecular connectivity in chemistry and drug research*, Academic Press, New York (**1976**).

[8] Kier, L. B. and Hall, L. H. *Molecular structure description: The Electrotopological state*, Academic Press, New York (**1999**).

[9] Taft, R. W. *Polar and steric substituent constants for aliphatic and o-benzoate groups from rates of esterification and hydrolysis of esters, J. Am. Chem. Soc.*, 71, 3129-3128 (**1952**).

[10] Taft, R.W. In: *Steric effects in organic chemistry*, Ed. Newman, M.S., Wiley, New York, pp 556-580 (**1956**).

[11] Verloop, A., Hoogenstraaten, W. and Tifter, J. In: *Drug design*, vol. 7, Ed. Arien's E. J., Academic Press, New York, pp 165-207 (**1976**).

[12] Selassie, C. D. *History of quantitative structure-activity relationships, In:*

Burger's medicinal chemistry and drug discovery, Vol.1, Ed. Abraham., D. J., Wiley-Interscience, New Jersey, pp 1-48 (2003).

CHAPTER 3

QSAR STUDIES

RESULTS AND DISCUSSION

3 QSAR STUDIES: RESULTS AND DISCUSSION

In recent years several MMP inhibitors were synthesized. A quantitative analysis of the biological activity and the physiochemical properties of these compounds will precisely determine the extent of the role played by different physiochemical and structural properties of the molecules that can lead them to strongly bind with the receptor. Further, the correlation equations (Eqs.) may be exploited to design a better compound.

In this chapter, we present the detailed QSAR studies on the following categories of MMP inhibitors.

Sulfonylated aminoacids and their hydroxamates [1-4]
Functionalized 4-aminoproline hydroxamates [17]
Anthranilic hydroxamic acid inhibitors [18-21]
Bicyclic heteroaryl hydroxamic acid analogs [23]
Pyranyl hydroxamic acid analogs [24,25]
Piperidine sulfonamide aryl hydroxamic acid analogs [26,27]
Acyclic hydroxamic acid analogs [28-31]
Piperazine, Piperidine and Diazepine hydroxamic acid analogs [32-35]
Benzodiazepine hydroxamic acid analogs [36,37]

The parameters such as E-state indices (S) and first-order valence molecular connectivity index ($^{1}\chi^{v}$) were calculated as per the procedure mentioned in the chapter 2. The hydrophobicity parameter ClogP was calculated using www.daylight.com domain, polarizability (Pol) and molar volume (MV) were calculated from www.acdlabs.com domain (Version 5) and their values are equally scaled. The hydrophobic constant π and the electronic constant σ (Hammett constant) of the substituents have been taken from the literature as referenced in chapter 2. The regression analysis was carried out using self generated QSAR software.

In all the QSAR that is going to be discussed, n is the number of data points, r is the correlation coefficient, r^2_{cv} is the square of cross-validated correlation coefficient obtained by leave-one-out (LOO) jackknife procedure, s is the standard deviation, and F is the F-ratio between the variances of calculated and observed activities (within parenthesis the figure refers to the F-value at 99% level). The data with ± sign within the parentheses refer to 95% confidence intervals for the coefficients of the variables as well as for the intercept.

All the compounds have been taken from the various sources as indicated by the references. Their results are discussed one by one.

3.1 Sulfonylated aminoacids and their hydroxamates

Recently in successive studies, Scozzafava and Supuran [1-4] reported the ChC inhibition potencies of the following series of sulfonylated amino acids and their hydroxamates.

(a) Sulfonylated N-(4-nitrobenzyl)-L-alanine derivatives (**1A**) and corresponding hydroxamates (**1B**) [1].

(b) Sulfonylated N-benzyl-L-valine derivatives (**2A**) and corresponding hydroxamates (**2B**) [2].

(c) Sulfonylated N- (2-chlorobenzyl)-L-alanine derivatives (**3A**) and corresponding hydroxamates (**3B**) [3].

(d) Sulfonylated N-benzyl-glycine derivatives (**4A**) and corresponding hydroxamates (**4B**) [4].

All these series of compounds (Figure 3.1) taken for QSAR study are listed in Tables 3.1 – 3.4, respectively, along with the physicochemical parameters that were found to be correlated with their ChC inhibition potencies. The enzyme inhibition constant K_i, observed as well as calculated from correlations obtained, are listed in Tables 3.5 – 3.8, respectively.

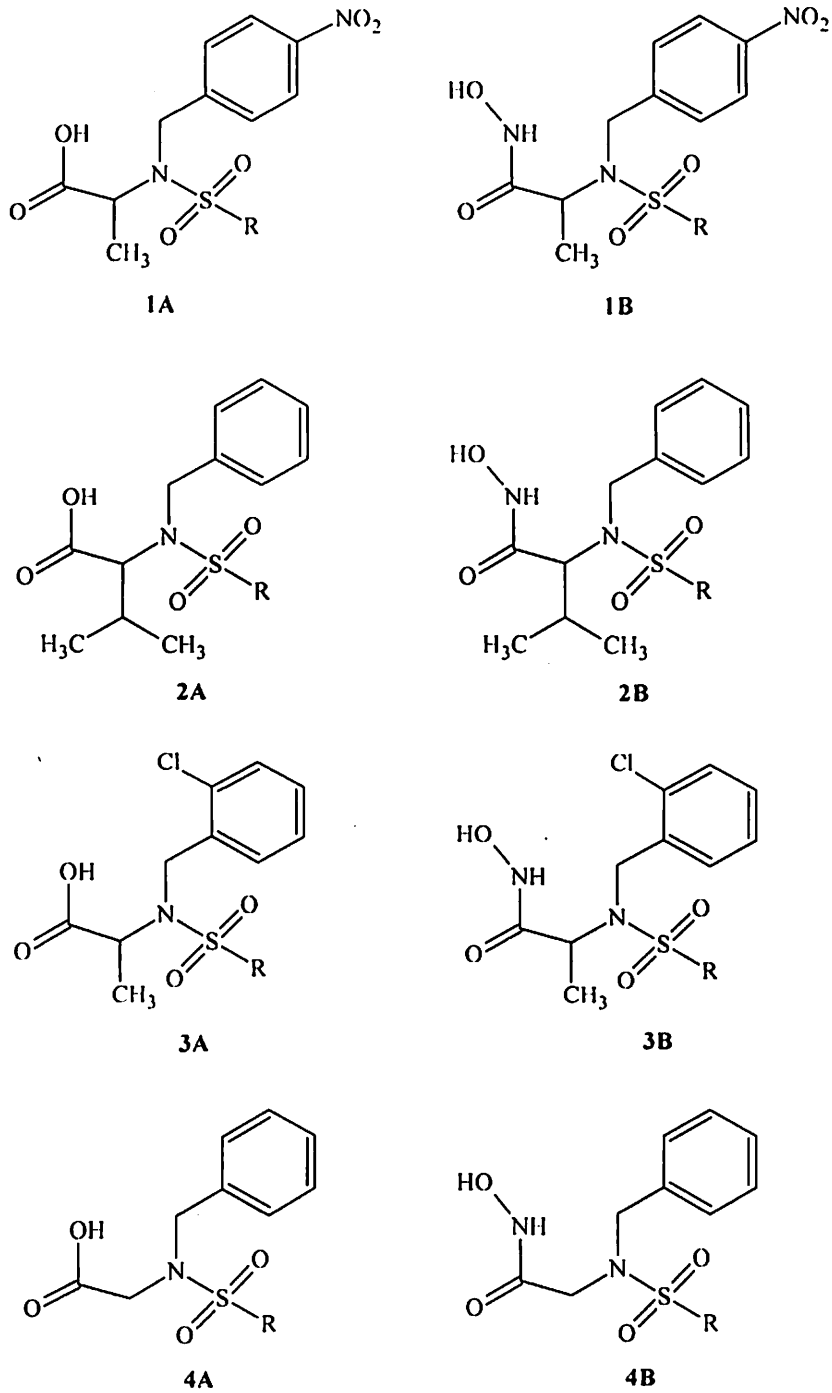


Figure 3.1. A series of sulfonylated aminoacids (**1A-4A**) and their hydroxamates derivatives (**1B-4B**)

Table 3.1. Sulfonylated N-(4-nitrobenzyl)-L-alanine derivatives (**1A and 1B**) with their E-state indices.

Compd	R	Series 1A		Series 1B		
		$S(_N)$	$S(_S)$	$S(_N)$	$S(_S)$	I
1	CH_3	0.941	-5.058	1.000	-5.073	0
2	CF_3	-0.101	-7.398	-0.042	-7.413	0
3	CCl_3	1.066	-5.324	1.125	-5.339	0
4	n-C_4F_9	-0.809	-8.920	-0.750	-8.935	0
5	n-C_8F_{17}	-1.247	-9.734	-1.188	-9.749	0
6	Me_2N	0.941	-5.410	1.000	-5.425	0
7	C_6H_5	0.978	-5.587	1.037	-5.603	0
8	$PhCH_2$	1.017	-5.440	1.076	-5.455	0
9	4-F-C_6H_4	0.865	-5.785	0.924	-5.800	0
10	4-Cl-C_6H_4	0.992	-5.612	1.051	-5.627	0
11	4-Br-C_6H_4	1.002	-5.598	1.061	-5.613	0
12	4-I-C_6H_4	1.004	-5.595	1.063	-5.610	0
13	4-CH_3-C_6H_4	0.987	-5.618	1.046	-5.633	0
14	4-O_2N-C_6H_4	0.831	-5.887	0.890	-5.902	0
15	3-O_2N-C_6H_4	0.787	-5.996	0.846	-6.011	0
16	2-O_2N-C_6H_4	0.721	-6.176	0.780	-6.191	0
17	3-Cl-4-O_2N-C_6H_3	0.850	-5.920	0.989	-5.936	0
18	4-AcNH-C_6H_4	0.921	-5.785	0.979	-5.800	0
19	4-BocNH-C_6H_4	0.910	-5.866	0.968	-5.881	0
20	3-BocNH-C_6H_4	0.892	-5.954	0.951	-5.969	0
21	4-Ac-C_6H_4	0.916	-5.776	0.975	-5.791	0
22	C_6F_5	0.120	-7.224	0.179	-7.239	1
23	3-CF_3- C_6H_4	0.645	-6.232	0.704	-6.247	1
24	2,5-$Cl_2C_6H_3$	1.027	-5.669	1.086	-5.684	0
25	4-CH_3O-C_6H_4	0.957	-5.692	1.015	-5.707	0
26	2,4,6-$(CH_3)_3$-C_6H_2	1.029	-5.742	1.088	-5.757	0
27	4-CH_3O-3-BocNH-C_6H_3	0.869	-6.055	0.927	-6.070	0
28	2-OH-3, 5-Cl_2-C_6H_2	0.878	-5.967	0.937	-5.982	0
29	3-HOOC-C_6H_4	0.817	-5.955	0.917	-5.888	0
30	4-HOOC-C_6H_4	0.853	-5.857	0.885	-5.986	0
31	1-Naphthyl	1.012	-5.799	1.071	-5.814	0
32	2-Naphthyl	1.001	-5.737	1.059	-5.752	0
33	5-Me_2N-1-Naphthyl	1.011	-5.782	1.070	-5.797	0
34	2-Thienyl	1.051	-5.395	1.110	-5.410	0
35	Quinoline-8-yl	1.006	-5.725	1.064	-5.740	0

Table 3.2. Sulfonylated N-benzyl-L-valine derivatives (**2A and 2B**) with their E-state indices.

Compd	R	Series 2A		Series 2B		
		$S_{(N)}$	$S_{(S)}$	$S_{(N)}$	$S_{(S)}$	I
1	CH_3	1.162	-4.962	1.221	-4.977	0
2	CF_3	0.120	-7.302	0.179	-7.317	0
3	CCl_3	1.287	-5.228	1.346	-5.243	0
4	n-C_4F_9	-0.588	-8.824	-0.529	-8.839	0
5	n-C_8F_{17}	-1.026	-9.638	-0.967	-9.653	0
6	Me_2N	1.162	-5.313	1.221	-5.328	0
7	C_6H_5	1.199	-5.491	1.258	-5.506	0
8	$PhCH_2$	1.238	-5.344	1.297	-5.359	0
9	4-F-C_6H_4	1.086	-5.688	1.145	-5.704	0
10	4-Cl-C_6H_4	1.213	-5.516	1.272	-5.531	0
11	4-Br-C_6H_4	1.223	-5.501	1.282	-5.516	0
12	4-I-C_6H_4	1.226	-5.498	1.284	-5.513	0
13	4-CH_3-C_6H_4	1.208	-5.522	1.267	-5.537	0
14	4-O_2N-C_6H_4	1.052	-5.791	1.111	-5.806	0
15	3-O_2N-C_6H_4	1.008	-5.899	1.067	-5.914	0
16	2-O_2N-C_6H_4	0.942	-6.080	1.001	-6.095	0
17	3-Cl-4-O_2N-C_6H_3	1.072	-5.824	1.130	-5.839	0
18	4-AcNH-C_6H_4	1.142	-5.689	1.200	-5.704	0
19	4-BocNH-C_6H_4	1.131	-5.770	1.189	-5.785	0
20	3-BocNH-C_6H_4	1.113	-5.857	1.172	-5.872	0
21	C_6F_5	0.341	-7.127	0.400	-7.142	1
22	3-CF_3- C_6H_4	0.866	-6.136	0.925	-6.151	1
23	2,5-$Cl_2C_6H_3$	1.248	-5.573	1.307	-5.588	0
24	4-CH_3O-C_6H_4	1.178	-5.596	1.236	-5.611	0
25	2,4,6-$(CH_3)_3$-C_6H_2	1.250	-5.646	1.309	-5.661	0
26	4-CH_3O-3-BocNH-C_6H_3	1.090	-5.959	1.149	-5.974	0
27	2-OH-3, 5-Cl_2-C_6H_2	1.099	-5.870	1.158	-5.885	0
28	3-HOOC-C_6H_4	1.038	-5.858	1.106	-5.890	0
29	4-HOOC-C_6H_4	1.074	-5.761	1.139	-5.792	0
30	1-Naphthyl	1.233	-5.703	1.292	-5.718	0
31	2-Naphthyl	1.222	-5.641	1.280	-5.656	0
32	5-Me_2N-1-Naphthyl	1.232	-5.685	1.291	-5.701	0
33	2-Thienyl	1.272	-5.298	1.331	-5.313	0

Table 3.3. Sulfonylated N-(2-chlorobenzyl)-L-alanine derivatives (**3A and 3B**) with their E-state indices.

Compd	R	Series 3A		Series 3B		
		$S(_N)$	$S(_S)$	$S(_N)$	$S(_S)$	I
1	CH_3	1.118	-4.901	1.176	-4.916	0
2	CF_3	0.076	-7.241	0.135	-7.256	0
3	CCl_3	1.243	-5.167	1.301	-5.182	0
4	n-C_4F_9	-0.632	-8.763	-0.573	-8.778	0
5	n-C_8F_{17}	-1.070	-9.577	-1.011	-9.592	0
6	Me_2N	1.118	-5.253	1.176	-5.268	0
7	C_6H_5	1.155	-5.431	1.213	-5.446	0
8	$PhCH_2$	1.194	-5.283	1.253	-5.298	0
9	4-F-C_6H_4	1.042	-5.628	1.100	-5.643	0
10	4-Cl-C_6H_4	1.168	-5.455	1.227	-5.470	0
11	4-Br-C_6H_4	1.179	-5.441	1.238	-5.456	0
12	4-I-C_6H_4	1.181	-5.438	1.240	-5.453	0
13	4-CH_3-C_6H_4	1.164	-5.461	1.223	-5.476	0
14	4-O_2N-C_6H_4	1.008	-5.730	1.066	-5.745	0
15	3-O_2N-C_6H_4	0.964	-5.839	1.023	-5.854	0
16	2-O_2N-C_6H_4	0.898	-6.019	0.956	-6.034	0
17	3-Cl-4-O_2N-C_6H_3	1.027	-5.764	1.086	-5.779	0
18	4-AcNH-C_6H_4	1.097	-5.628	1.156	-5.643	0
19	4-BocNH-C_6H_4	1.086	-5.710	1.145	-5.725	0
20	3-BocNH-C_6H_4	1.369	-5.797	1.127	-5.812	0
21	C_6F_5	0.297	-7.067	0.355	-7.082	1
22	3-CF_3- C_6H_4	0.822	-6.075	0.880	-6.090	1
23	2,5-$Cl_2C_6H_3$	1.204	-5.512	1.263	-5.527	0
24	4-CH_3O-C_6H_4	1.133	-5.535	1.192	-5.550	0
25	2,4,6-$(CH_3)_3$-C_6H_2	1.206	-5.585	1.264	-5.600	0
26	4-CH_3O-3-BocNH-C_6H_3	1.045	-5.898	1.104	-5.913	0
27	2-OH-3, 5-Cl_2-C_6H_2	1.055	-5.810	1.113	-5.825	0
28	3-HOOC-C_6H_4	0.994	-5.798	1.061	-5.830	0
29	4-HOOC-C_6H_4	1.030	-5.700	1.094	-5.731	0
30	1-Naphthyl	1.189	-5.642	1.248	-5.657	0
31	2-Naphthyl	1.177	-5.580	1.236	-5.595	0
32	5-Me_2N-1-Naphthyl	1.188	-5.625	1.246	-5.640	0
33	2-Thienyl	1.228	-5.238	1.286	-5.253	0
34	Quinoline-8-yl	1.182	-5.568	1.241	-5.583	0

Table 3.4. Sulfonylated N-benzyl-glycine derivatives (**4A and 4B**) with their E-state indices.

		Series 4A		Series 4B		
Compd	R	$S(_N)$	$S(_S)$	$S(_N)$	$S(_S)$	I
1	CH_3	1.046	-4.796	1.105	-4.811	0
2	CF_3	0.005	-7.136	0.063	-7.151	0
3	CCl_3	1.171	-5.062	1.230	-5.077	0
4	n-C_4F_9	-0.703	-8.658	-0.645	-8.673	0
5	n-C_8F_{17}	-1.142	-9.472	-1.083	-9.487	0
6	Me_2N	1.046	-5.148	1.105	-5.163	0
7	C_6H_5	1.083	-5.326	1.142	-5.341	0
8	$PhCH_2$	1.123	-5.178	1.181	-5.194	0
9	4-F-C_6H_4	0.970	-5.523	1.029	-5.538	0
10	4-Cl-C_6H_4	1.097	-5.350	1.156	-5.365	0
11	4-Br-C_6H_4	1.108	-5.336	1.166	-5.351	0
12	4-I-C_6H_4	1.110	-5.333	1.169	-5.348	0
13	4-CH_3-C_6H_4	1.093	-5.356	1.151	-5.363	0
14	4-O_2N-C_6H_4	0.936	-5.625	0.995	-5.640	0
15	3-O_2N-C_6H_4	0.893	-5.734	0.951	-5.749	0
16	2-O_2N-C_6H_4	0.826	-5.914	0.885	-5.929	0
17	3-Cl-4-O_2N-C_6H_3	0.956	-5.659	1.015	-5.674	0
18	4-AcNH-C_6H_4	1.026	-5.523	1.085	-5.539	0
19	4-BocNH-C_6H_4	1.015	-5.605	1.074	-5.620	0
20	3-BocNH-C_6H_4	0.997	-5.692	1.056	-5.707	0
21	C_6F_5	0.225	-6.962	0.284	-6.977	1
22	3-CF_3- C_6H_4	0.750	-5.970	0.809	-5.985	1
23	2,5-$Cl_2C_6H_3$	1.133	-5.407	1.191	-5.423	0
24	4-CH_3O-C_6H_4	1.062	-5.430	1.121	-5.445	0
25	2,4,6-$(CH_3)_3$-C_6H_2	1.134	-5.480	1.193	-5.495	0
26	4-CH_3O-3-BocNH-C_6H_3	0.974	-5.793	1.033	-5.808	0
27	2-OH-3, 5-Cl_2-C_6H_2	0.983	-5.705	1.042	-5.720	0
28	3-HOOC-C_6H_4	0.922	-5.693	-	-	-
29	4-HOOC-C_6H_4	0.959	-5.595	-	-	-
30	1-Naphthyl	1.117	-5.537	1.176	-5.553	0
31	2-Naphthyl	1.106	-5.475	1.165	-5.490	0
32	5-Me_2N-1-Naphthyl	1.116	-5.520	1.175	-5.535	0
33	2-Thienyl	1.156	-5.133	1.215	-5.148	0

Table 3.5. Observed and calculated ChC inhibition potencies of compounds of Table 3.1. Observed activities have been taken from ref. [1].

Compd	Series 1A			Series 1B		
	Obsd	Calcd Eq. 1	Loo	Obsd	Calcd Eq. 2	Loo
1	4.74[a]	3.8	-	7.12[b]	6.16	-
2	5.33	5.02	4.93	7.12	7.42	7.40
3	5.29	4.90	4.83	7.28	7.31	7.28
4	5.64	5.69	5.71	7.96	8.08	7.99
5	5.74	5.82	5.90	8.15	8.20	8.01
6	4.44	4.60	4.68	7.16	7.01	6.89
7	4.68[a]	5.15	-	7.27	7.56	7.55
8	4.82	4.97	4.99	7.30	7.38	7.35
9	5.00	5.15	5.16	7.46	7.56	7.54
10	5.05	5.26	5.27	7.49	7.67	7.65
11	5.00	5.27	5.28	7.52	7.68	7.66
12	4.92	5.27	5.29	7.43	7.68	7.66
13	4.89	5.26	5.28	7.44	7.66	7.65
14	5.28	5.25	5.25	8.00[b]	7.63	-
15	5.26	5.33	5.33	7.92	7.73	7.69
16	5.32	5.48	5.49	7.89	7.88	7.84
17	5.48	5.40	5.40	8.05	8.12	8.11
18	5.51	5.38	5.37	7.96	7.78	7.74
19	5.62	5.52	5.51	8.00	7.92	7.89
20	5.59	5.64	5.65	8.10	8.05	8.02
21	5.68	5.34	5.32	8.05	7.74	7.70
22	6.40	6.55	6.71	8.30	7.89	7.83
23	6.52	6.37	6.21	8.22	7.71	7.67
24	5.44	5.53	5.53	7.89	7.94	7.92
25	5.28	5.31	5.31	7.68	7.71	7.68
26	5.22	5.70	5.76	7.77	8.11	8.12
27	5.68	5.78	5.79	8.10	8.18	8.17
28	5.60	5.62	5.62	7.92	8.02	8.01
29	5.70	5.35	5.34	8.05	7.73	7.69
30	5.85[a]	5.27	-	8.22[b]	7.70	-
31	5.92	5.76	5.74	8.15	8.17	8.16
32	5.89	5.58	5.56	8.10	7.98	7.96
33	5.96	5.72	5.70	8.15	8.13	8.11
34	5.68[a]	5.00	-	7.96[b]	7.38	-
35	5.92	5.57	5.55	8.10	7.98	7.95

[a]Not included in the derivation of Eq. 1.
[b]Not included in the derivation of Eq. 2.

Table 3.6. Observed and calculated ChC inhibition potencies of compounds of Table 3.2. Observed activities have been taken from ref [2].

Compd	Series 2A			Series 2B		
	Obsd	Calcd Eq. 3	Loo	Obsd	Calcd Eq. 4	Loo
1	4.74[a]	4.01	-	7.00[b]	6.15	-
2	5.48	5.07	4.94	7.33	7.36	7.36
3	5.25	4.85	4.79	7.28	7.30	7.30
4	5.49	5.67	5.76	8.00	8.02	8.02
5	5.72	5.81	5.91	8.10	8.12	8.15
6	4.39	4.63	4.74	7.19	6.98	6.88
7	4.70	5.06	5.08	7.27	7.56	7.58
8	4.82	4.91	4.92	7.40	7.37	7.37
9	4.92	5.07	5.08	7.38	7.55	7.57
10	4.96	5.14	5.15	7.36	7.67	7.69
11	5.00	5.15	5.15	7.44	7.68	7.69
12	5.00	5.15	5.16	7.52	7.68	7.69
13	4.82	5.14	5.15	7.48	7.67	7.68
14	5.30	5.15	5.15	7.82	7.66	7.65
15	5.29	5.22	5.21	7.96	7.73	7.72
16	5.28	5.34	5.34	7.74	7.88	7.89
17	5.52	5.27	5.26	7.96	7.81	7.81
18	5.46	5.24	5.23	8.00	7.78	7.78
19	5.62	5.35	5.34	8.10	7.93	7.92
20	5.64	5.45	5.44	8.15	8.07	8.06
21	6.40	6.41	6.42	8.30	8.34	8.38
22	6.22	6.21	6.20	8.22	8.18	8.14
23	5.40	5.35	5.34	7.96	7.96	7.96
24	5.20	5.18	5.18	7.77	7.71	7.71
25	5.21	5.49	5.52	7.75[b]	5.14	-
26	5.48	5.57	5.58	8.15	8.21	8.22
27	5.49	5.43	5.43	8.15	8.04	8.03
28	5.35	5.23	5.22	8.05	7.83	7.82
29	5.62[a]	5.17	-	8.10[b]	7.74	-
30	5.48	5.54	5.55	8.05	8.20	8.22
31	5.85[a]	5.40	-	8.22	8.00	7.98
32	5.70	5.50	5.48	8.10	8.16	8.16
33	5.68[a]	4.93	-	8.00[b]	7.40	-

[a]Not included in the derivation of Eq. 3.
[b]Not included in the derivation of Eq. 4.

Table 3.7. Observed and calculated ChC inhibition potencies of compounds of Table 3.3. Observed activities have been taken from ref [3].

Compd	Series 3A			Series 3B		
	Obsd	Calcd Eq. 5	Loo	Obsd	Calcd Eq. 6	Loo
1	4.68	4.52	4.41	7.04[b]	6.06	-
2	5.48	5.27	5.23	7.12	7.30	7.35
3	5.28	5.01	4.99	7.15	7.23	7.24
4	5.52	5.70	5.79	7.96	7.97	7.97
5	5.82	5.84	5.86	8.10	8.08	8.06
6	4.40	4.89	4.96	7.11	6.91	6.82
7	4.62[a]	5.14	-	7.24	7.49	7.51
8	4.80	5.05	5.07	7.27	7.31	7.31
9	4.92	5.16	5.18	7.44	7.49	7.49
10	4.89	5.19	5.20	7.46	7.61	7.62
11	5.00	5.19	5.20	7.48	7.62	7.63
12	5.00	5.19	5.20	7.52	7.62	7.63
13	4.74	5.19	5.21	7.35	7.61	7.62
14	5.29	5.22	5.21	7.82	7.59	7.58
15	5.30	5.26	5.26	7.96	7.67	7.66
16	5.31	5.34	5.34	7.80	7.82	7.82
17	5.51	5.28	5.28	8.00	7.76	7.75
18	5.52	5.26	5.25	7.96	7.73	7.72
19	5.57	5.33	5.32	8.05	7.88	7.87
20	5.62	5.89	6.07	8.10	8.01	8.01
21	6.40	6.44	6.48	8.30	8.35	8.40
22	6.30	6.26	6.22	8.22	8.17	8.13
23	5.39	5.31	5.29	7.82	7.90	7.90
24	5.22	5.22	5.22	7.66	7.65	7.66
25	5.17	5.39	5.41	7.77	8.08	8.11
26	5.52	5.46	5.45	8.10	8.16	8.16
27	5.62	5.38	5.37	8.05	7.98	7.98
28	5.39	5.27	5.26	8.10[b]	7.77	-
29	5.42	5.22	5.21	8.15[b]	7.67	-
30	5.80	5.43	5.40	8.10	8.15	8.16
31	5.82[a]	5.34	-	8.05	7.95	7.94
32	5.68	5.41	5.39	8.00	8.10	8.11
33	5.62[a]	5.06	-	7.96[b]	7.33	-
34	5.70[a]	5.33	-	8.15	7.94	7.92

[a]Not included in the derivation of Eq. 5.
[b]Not included in the derivation of Eq. 6.

Table 3.8. Observed and calculated ChC inhibition potencies of compounds of Table 3.4. Observed activities have been taken from ref [4].

Compd	Series 4A			Series 4B		
	Obsd	Calcd Eq. 7	Loo	Obsd	Calcd Eq. 8	Loo
1	4.60[a]	3.75	-	6.95[b]	6.19	-
2	5.30	4.96	4.85	7.28	7.30	7.31
3	5.22[a]	4.7	-	7.29	7.21	7.20
4	5.52	5.65	5.71	7.88	7.92	7.93
5	5.70	5.81	5.93	8.04	8.03	7.97
6	4.33	4.46	4.52	7.02	6.93	6.89
7	4.62	4.93	4.96	7.27	7.44	7.45
8	4.72	4.77	4.78	7.32	7.28	7.27
9	4.82	4.95	4.96	7.29	7.44	7.45
10	4.85	5.03	5.04	7.35	7.54	7.56
11	4.85	5.04	5.05	7.41	7.55	7.56
12	4.89	5.04	5.04	7.52	7.56	7.56
13	4.77	5.03	5.04	7.36	7.52	7.53
14	5.22	5.04	5.03	7.80[b]	7.53	-
15	5.30	5.12	5.11	7.82	7.60	7.59
16	5.15	5.25	5.26	7.62	7.74	7.75
17	5.52[a]	5.18	-	7.92	7.68	7.67
18	5.40	5.14	5.13	7.89	7.65	7.64
19	5.52	5.27	5.25	8.00	7.78	7.77
20	5.69	5.38	5.35	8.05	7.90	7.89
21	6.15	6.27	6.27	8.22	8.27	8.22
22	6.15	6.03	6.03	8.15	8.10	8.10
23	5.30	5.26	5.26	7.67	7.79	7.80
24	5.15	5.07	5.07	7.57	7.58	7.59
25	5.15	5.41	5.43	7.82	7.95	7.97
26	5.52	5.50	5.50	8.10	8.03	8.02
27	5.40	5.36	5.36	8.05[b]	7.87	-
28	5.30	5.13	5.12	-	-	-
29	5.30	5.06	5.06	-	-	-
30	5.40	5.47	5.48	7.96	8.01	8.02
31	5.40	5.31	5.30	7.92	7.84	7.83
32	5.30	5.43	5.45	7.89	7.97	7.98
33	5.40[a]	4.79	-	7.80[b]	7.30	-

[a]Not included in the derivation of Eq. 7.
[b]Not included in the derivation of Eq. 8.

For all the series of compounds, the inhibition constants were found to be significantly correlated with the E-state indices of the sulfur and nitrogen and an indicator variable I used for an R–substituent like C_6F_5 or 3-CF_3-C_6H_4 The correlations obtained were as follows:

1A

$$\log (1/K_i) = 3.933(\pm1.385)S_N - 2.271(\pm0.767)S_S + 1.061(\pm0.372)I - 11.385(\pm5.703)$$

$$n = 31,\ r = 0.858,\ r^2_{cv} = 0.65,\ s = 0.24,\ F_{3,27} = 25.03(4.60) \quad (1)$$

1B

$$\text{Log } (1/K_i) = 4.060(\pm0.946)S_N - 2.312(\pm0.524)S_S + 0.510(\pm0.263)I - 9.633(\pm3.962)$$

$$n = 31,\ r = 0.886,\ r^2_{cv} = 0.60,\ s = 0.17,\ F_{3,27} = 32.92(4.60) \quad (2)$$

2A

$$\log (1/K_i) = 2.980(\pm1.250)S_N - 1.781(\pm0.689)S_S + 0.996(\pm0.330)I - 8.293(\pm5.331)$$

$$n = 29,\ r = 0.875,\ r^2_{cv} = 0.68,\ s = 0.22,\ F_{3,25} = 27.22(4.68) \quad (3)$$

2B

$$\log (1/K_i) = 4.171(\pm1.007)S_N - 2.374(\pm0.554)S_S + 0.480(\pm0.261)I - 10.763(\pm4.358)$$

$$n = 29,\ r = 0.891,\ r^2_{cv} = 0.75,\ s = 0.17,\ F_{3,25} = 32.06(4.68) \quad (4)$$

3A

$$\log (1/K_i) = 1.676(\pm0.808)S_N - 1.067(\pm0.443)S_S + 0.988(\pm0.375)I - 2.588(\pm3.360)$$

$$n = 30,\ r = 0.849,\ r^2_{cv} = 0.64,\ s = 0.25,\ F_{3,26} = 22.30(4.64) \quad (5)$$

3B

$$\log (1/K_i) = 4.218(\pm0.947)S_N - 2.404(\pm0.523)S_S + 0.539(\pm0.257)I - 10.718(\pm4.041)$$

$$n = 30,\ r = 0.899,\ r^2_{cv} = 0.77,\ s = 0.17,\ F_{3,26} = 36.69(4.64) \quad (6)$$

4A

$$\log (1/K_i) = 3.329(\pm1.170)S_N - 1.998(\pm0.649)S_S + 0\ 920(\pm0.301)I - 9.313(\pm4.778)$$

$$n = 29,\ r = 0.893,\ r^2_{cv} = 0.72,\ s = 0.20,\ F_{3,25} = 32.96(4.60) \quad (7)$$

4B

$$\log (1/K_i) = 3.655(\pm0.831)S_N - 2.102(\pm0.459)S_S + 0.522(\pm0.219)I - 7.960(\pm3.432)$$

$$n = 27,\ r = 0.918,\ r^2_{cv} = 0.81,\ s = 0.14,\ F_{3,23} = 40.85(4.76) \quad (8)$$

Now all the above equations exhibit parallel correlations, indicating that in all the cases the inhibition potency of the compounds will increase with the increase in the E-state index of the nitrogen and will decrease with the increase in the E-state index of the sulfur. Since E-state indices are the measure of the availability of the π and / or lone pair electrons on the atoms, it is certain that both nitrogen and sulfur might be playing some electronic roles in the interaction of the compounds with the receptors. Nitrogen can be assumed to be involved in some charge-transfer phenomenon with the enzymes where the stability of charge-transfer complex formed will depend upon the value of S_N, i.e., on the availability of π or the lone pair electrons on the nitrogen. Similarly, the sulfur can be assumed to be involved in some charge-charge repulsion interaction with the receptors, where increase in the availability of π or lone pair electrons will destabilize the bonding due to the increase in the repulsion. Such type of roles of nitrogen and sulfur have been described by us in the inhibition of MMPs also [5-7].

Similarly, as some of our previous studies, this study also points out a specific role of C_6F_5- and 3-CF_3-C_6H_4 like R–substituents for which an indicator parameter I has been used with a value of unity. A positive coefficient of this parameter in all the equations suggests that such R–substituents would be beneficial to the inhibition potency for all the series of compounds discussed here. However, the point to be noted is that in all acid series (**1A-4A**) the coefficient of I are essentially the same and similarly in all the hydroxamate series (**1B-4B**) they are essentially the same. Another point, which is more important, is that the coefficient of I in any **A** series is just the double of that in corresponding **B** series. Thus, in all **A** series the C_6F_5 and 3-CF_3-C_6H_4 substituents are equally twofold more effective (in log unit) than in the B series.

Since the ChC enzyme catalyzes the cleavage of the Xaa-Gly (Xaa: amino acid residue) peptide bond of the repeating sequence of the collagen: -Gly-Pro-Xaa-Gly-Pro-Xaa-, it appears that the S_3', S_2', and S_1' subsites* of the enzyme are occupied by Gly, Pro, and Xaa, respectively [8-14]. In the design of the ChC inhibitors mentioned here, the following structural elements were opted by Scozzafava and Supuran, which were based

on strong MMP inhibitory properties of some arylsulphonyl-aminohydroxamic acids studied by Jeng et al. [15] and Hanessian et al. [16].

1. a strong zinc-binding function (of the carboxylic acids or better hydroxamic acid types).
2. a relatively compact spacer between this function and the rest of the molecule, i.e., any amino acid moiety.
3. a variant of the already optimized benzyl group to interact with S_2' site.
4. an arylsulfonyl moiety to interact with S_3' site.

All these structural elements for a hydroxamate and their interactions with ChC can be schematically shown as in Figure 3.2.

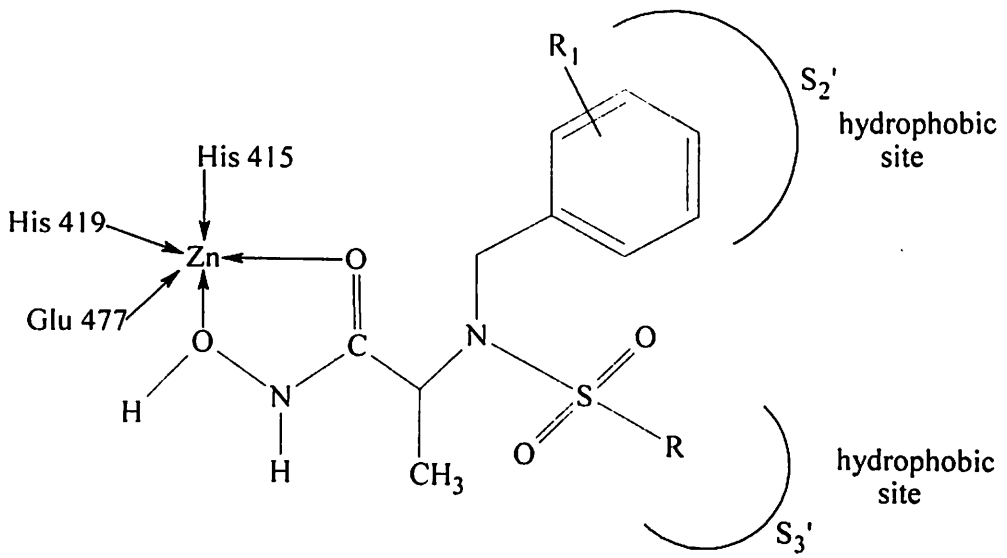


Figure 3.2. A model showing the binding features of a hydroxamate within the ChC.

*In a standard nomenclature, S_n is used to represent a binding site of the enzyme and a P_n to represent the corresponding binding group in substrate[5]. If the enzyme has structural symmetry, then the symmetrical binding sites are represented by S_n' and the corresponding binding groups in the substrate by P_n' [5]

Now the nitrogen and sulfur, that are indicated in this study to play a dominant roles in the binding, appear to seek some electronic sites in the enzyme to interact with, for which a typical conformation of the molecule may be required. An R-substituent of the type C_6F_5 or 3-CF_3-C_6H_4 might interact with the enzyme through the hydrogen bond formation between fluorine, present specifically at the 3-position, and some hydrogen bond donor site of the enzyme, otherwise an R-substituent present at P_3' site is supposed to have an hydrophobic interaction with the enzyme and so is the case with the benzyl moiety in P_2' site.

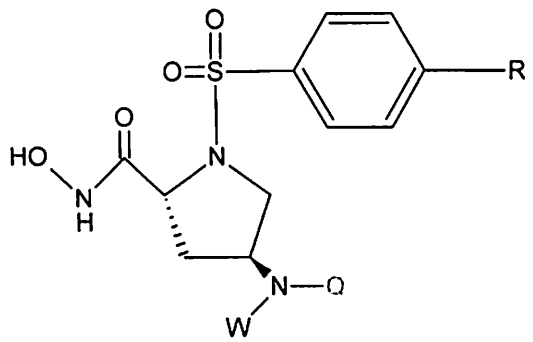
In the derivation of all the equations, some compounds as indicated in Tables (3.5-3.8), were excluded since they were exhibiting aberrant behaviours. Since all the outliers are not common in all the tables, it is difficult to assign the reason for the aberrant behaviour of each and every compound. However, there are two compounds, first and last, in each table with R = CH_3 and 2-thienyl, respectively, that are exhibiting aberrant behaviour in all the series (the exception is only Table 3.7, where compound 1 is not an outlier). These two compounds in all the series have much higher observed potency than predicted for them. The only explanation that can be given for this discrepancy is that their R–substituents might be having a good steric fit with the active site (S_3') of the receptor.

3.2 Functionalized 4-Aminoproline Hydroxamates

Natchus et al. [17] synthesised a series of functionalized 4-aminoproline hydroxamates and studied the MMP inhibition activity. All these compounds are listed in Tables 3.9 – 3.12 respectively, along with their physicochemical parameters that were found to be correlated with their MMP inhibition potencies. The inhibition potencies of compounds, observed as well as calculated from correlations obtained, are listed in Tables 3.13 – 3.16, respectively. In these Tables, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme.

If we look at Tables 3.9 and 3.10, we find that the two series of compounds differ only with respect to the nature of Q moiety attached to the nitrogen of the amide group present at the 4-position. In Table 3.10, all the compounds have Q that contains carbonyl group, while a very few compounds in Table 3.9 have Q that contains carbonyl group. The Q in most of the cases in Table 3.9 has sulfonyl group. We have calculated $^{1}\chi^{v}$ for the whole 4-amide group in both the series ($^{1}\chi^{v}_{N}$) and that of R-substituent of the phenyl ring ($^{1}\chi^{v}_{R}$). Both the series were then combined and the following correlations were obtained for the inhibition of the various MMPs with the use of activity data as given in Tables 3.13 and 3.14.

Table 3.9. A series of substituted amines and different structural variables.



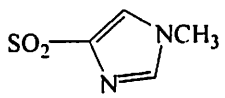
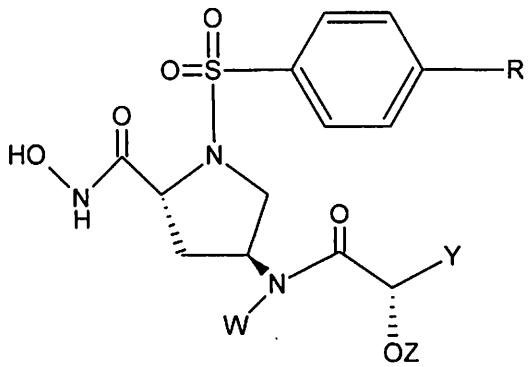
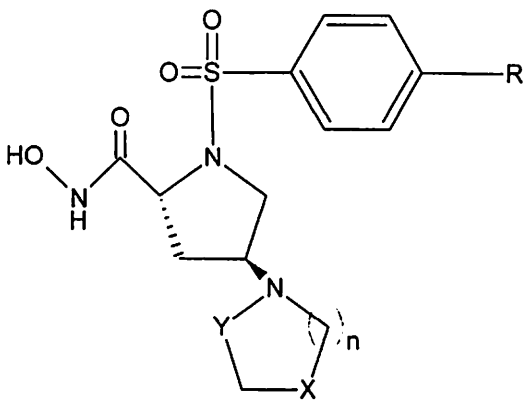
Compd	Q	W	R	$^{1}\chi^{v}_{N}$	$^{1}\chi^{v}_{R}$	S_S	I_W
1	H	H	OCH_3	0.000	0.612	-5.304	0
2	H	H	O^nBu	0.000	2.200	-5.340	0
3	$(CH_2)_2CH_3$	H	OCH_3	1.561	0.612	-5.321	0
4	$(CH_2)_2Ph$	H	OCH_3	2.961	0.612	-5.399	0
5	SO_2CH_3	H	OCH_3	2.836	0.612	-5.545	0
6	SO_2CH_3	H	O^nBu	2.836	2.200	-5.601	0
7	SO_2CH_3	H	O-4-Pyr	2.836	2.169	-5.673	0
8	SO_2CH_3	CH_3	OCH_3	3.219	0.612	-5.569	1
9	SO_2CH_3	CH_2-3-Pyr	OCH_3	5.202	0.612	-5.677	1
10	SO_2CH_3	$CH_2CH_2CH_3$	OCH_3	4.295	0.612	-5.602	1
11	SO_2-p-$C_6H_4OCH_3$	H	OCH_3	4.658	0.612	-5.676	0
12		H	O^nBu	3.958	2.200	-5.694	0
13	CO-p-Ph-Ph	H	OCH_3	4.686	0.612	-5.599	0
14	$CONHCH_3$	H	OCH_3	1.204	0.612	-5.480	0
15	CO^iPr	CH_2-3-Pyr	OCH_3	4.301	0.612	-5.613	1
16	$COCH_2OCH_3$	H	O^nPr	1.505	1.700	-5.529	0
17	$COCH_2OCH_3$	H	O^nBu	1.505	2.200	-5.539	0

Table 3.10. A series of lactic acid amide derivatives and different structural variables.



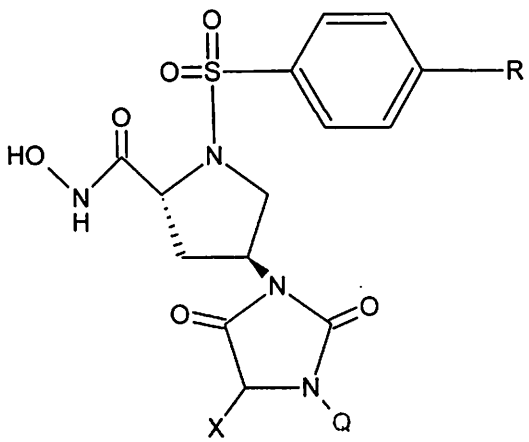
Compd	W	Y	Z	R	$^{1}\chi^{v}_{N}$	$^{1}\chi^{v}_{R}$	S_S	I_W
18	H	CH_3	CH_2Ph	OCH_3	4.109	0.612	-5.656	0
19	H	CH_2Ph	CH_2Ph	OCH_3	6.204	0.612	-5.732	0
20	^{n}Pr	CH_3	H	OCH_3	2.657	0.612	-5.668	1
21	^{n}Pr	CH_2CH_2Ph	H	OCH_3	5.670	0.612	-5.744	1
22	H	CH_3	H	$O^{n}Pr$	1.578	1.700	-5.638	0
23	H	CH_3	H	$O^{n}Bu$	1.578	2.200	-5.647	0
24	H	^{i}Pr	H	$O^{n}Bu$	2.489	2.200	-5.676	0
25	H	$CH_2{}^{i}Pr$	H	$O^{n}Bu$	2.972	2.200	-5.682	0

Table 3.11. A series of MMP inhibitors containing heterocyclic scaffolds and different structural variables.



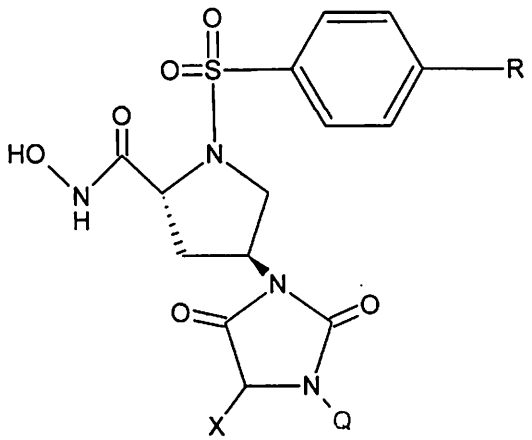
Compd	N	Y	X	R	$^{1}\chi^{v}_{N}$	$^{1}\chi^{v}_{R}$	S_S	I_Y	I_R
26	2	CH_2	CH_2	OMe	2.633	0.612	-5.561	0	1
27	2	CH_2	CH_2	O^{n}Pr	2.633	1.700	-5.587	0	1
28	2	CH_2	CH_2	^{n}Pent	2.633	2.561	-5.542	0	1
29	2	CH_2	CH_2	OPh	2.633	2.319	-5.659	0	1
30	2	CH_2	O	OMe	2.210	0.612	-5.593	0	1
31	2	CH_2	O	O^{n}Pr	2.210	1.700	-5.619	0	1
32	2	CH_2	O	O^{n}Bu	2.210	1.782	-5.628	0	1
33	2	CH_2	O	O^{n}Pent	2.210	2.561	-5.573	0	1
34	2	CH_2	O	OPh	2.210	2.319	-5.690	0	1
35	2	CH_2	SO_2	OMe	4.364	0.612	-5.707	0	1
36	2	CH_2	SO_2	O^{n}Bu	4.364	1.782	-5.743	0	1
37	1	CH_2	CH_2	O^{n}Pr	2.133	1.700	-5.571	0	1
38	1	CH_2	CH_2	O-4-C_6H_4F	2.133	2.419	-5.701	0	1
39	1	CH_2	CH_2	OPh	2.133	2.319	-5.642	0	1
40	1	SO_2	CH_2	OMe	3.729	0.612	-5.783	1	1
41	1	SO_2	CH_2	O^{n}Pr	3.729	1.700	-5.809	1	1
42	1	SO_2	CH_2	O^{n}Bu	3.729	1.782	-5.819	1	1

Table 3.12. A series of MMP inhibitors containing hydantoin moieties and different structural variables.



Compd	Q	X	R	$^{1}\chi^{v}_{N}$	$^{1}\chi^{v}_{R}$	S_S	I_Y	I_R
43	CH_3	H	OMe	2.196	0.612	-5.857	1	1
44	CH_3	H	OEt	2.196	1.200	-5.872	1	1
45	CH_3	H	O^nPr	2.196	1.200	-5.884	1	1
46	CH_3	H	O^nBu	2.196	1.782	-5.893	1	1
47	CH_3	H	$OCH_2CH(CH_3)_2$	2.196	2.056	-5.901	1	1
48	CH_3	H	$OCH_2CH_2OCH_3$	2.196	1.690	-5.918	1	0
49	CH_3	H	OPh	2.196	2.319	-5.955	1	1
50	CH_3	H	O-4-Pyr	2.196	2.169	-5.965	1	1
51	H	SCH_3	O^nBu	3.614	1.782	-5.865	1	1
52	H	$(CH_3)_2$	O^nBu	2.829	1.782	-5.887	1	1
53	$CH_2CH{=}CH_2$	H	O^nPr	2.882	1.700	-5.921	1	1
54	$CH_2CH{=}CH_2$	H	O^nBu	2.882	1.782	-5.931	1	1
55	$CH_2CH{=}CH_2$	H	$OCH_2CH_2OCH_3$	2.882	1.690	-5.955	1	0
56	$CH_2CH_2CH_3$	H	O^nBu	3.272	1.782	-5.915	1	1
57	$CH_2CH_2CH_3$	H	$OCH_2CH_2OCH_3$	3.272	1.690	-5.939	1	0

Table 3.12. A series of MMP inhibitors containing hydantoin moieties and different structural variables.



Compd	Q	X	R	$^{1}\chi^{v}_{N}$	$^{1}\chi^{v}_{R}$	S_S	I_Y	I_R
43	CH_3	H	OMe	2.196	0.612	-5.857	1	1
44	CH_3	H	OEt	2.196	1.200	-5.872	1	1
45	CH_3	H	O^{n}Pr	2.196	1.200	-5.884	1	1
46	CH_3	H	O^{n}Bu	2.196	1.782	-5.893	1	1
47	CH_3	H	$OCH_2CH(CH_3)_2$	2.196	2.056	-5.901	1	1
48	CH_3	H	$OCH_2CH_2OCH_3$	2.196	1.690	-5.918	1	0
49	CH_3	H	OPh	2.196	2.319	-5.955	1	1
50	CH_3	H	O-4-Pyr	2.196	2.169	-5.965	1	1
51	H	SCH_3	O^{n}Bu	3.614	1.782	-5.865	1	1
52	H	$(CH_3)_2$	O^{n}Bu	2.829	1.782	-5.887	1	1
53	$CH_2CH{=}CH_2$	H	O^{n}Pr	2.882	1.700	-5.921	1	1
54	$CH_2CH{=}CH_2$	H	O^{n}Bu	2.882	1.782	-5.931	1	1
55	$CH_2CH{=}CH_2$	H	$OCH_2CH_2OCH_3$	2.882	1.690	-5.955	1	0
56	$CH_2CH_2CH_3$	H	O^{n}Bu	3.272	1.782	-5.915	1	1
57	$CH_2CH_2CH_3$	H	$OCH_2CH_2OCH_3$	3.272	1.690	-5.939	1	0

Table 3.13. Observed and calculated MMP inhibition potencies of compounds of Table 3.9.

	log ($1/IC_{50}$)														
	MMP-1			MMP-2			MMP-3			MMP-7			MMP-13		
Compd	Obsd	Calcd Eq. (9)	Loo	Obsd	Calcd Eq. (10)	Loo	Obsd	Calcd Eq. (11)	Loo	Obsd	Calcd Eq. (12)	Loo	Obsd	Calcd Eq. (13)	Loo
1	6.60	6.60	6.60	8.22	8.37	8.56	7.64	7.77	7.87	5.37	5.44	5.50	8.30	8.33	8.35
2	6.42	6.15	6.17	-	8.37	-	8.10	7.88	7.87	-	5.37	-	-	8.93	-
3	6.82	6.60	6.56	-	8.68	-	7.06	7.17	7.73	5.66	5.68	5.70	8.30	8.43	8.48
4	6.25	6.60	6.66	9.00	8.97	8.96	7.24	7.01	7.11	5.85	5.78	5.73	9.00[e]	8.52	-
5	6.59	6.60	6.60	8.70	8.94	8.98	7.38	7.47	6.85	5.57	5.49	5.47	8.70	8.52	8.47
6	5.89	6.15	6.24	9.10	8.94	8.92	7.80	7.63	7.48	5.41	5.38	5.37	9.16	9.12	9.11
7	6.35	6.15	6.18	-	8.94	-	7.66	7.85	7.61	-	5.25	-	9.10	9.11	9.11
8	7.72	7.35	7.27	-	9.02	-	8.22	8.12	7.87	6.28[d]	5.51	-	9.30	9.08	9.01
9	7.13	7.35	7.10	8.70[b]	9.42	-	8.22	8.29	8.09	5.57	5.66	5.72	9.00	9.21	9.27
10	7.48	7.35	6.62	9.10	9.24	9.26	8.00	8.09	8.31	6.04[d]	5.65	-	9.10	9.15	9.16
11	6.46	6.60	6.20	8.52[b]	9.31	-	7.44	7.63	8.11	5.52	5.56	5.58	8.70	8.64	8.61
12	6.16	6.15	6.32	-	9.17	-	8.22[c]	7.72	-	-	5.40	-	-	9.19	-
13	-	6.60	-	-	9.32	-	6.40[c]	7.39	-	-	5.71	-	-	8.63	-
14	5.51[a]	6.60	-	-	8.61	-	6.52[c]	7.76	-	-	5.32	-	7.57[e]	8.41	-
15	5.57[a]	7.35	-	8.66[b]	9.24	-	8.00	8.12	7.67	-	5.61	-	7.77[e]	9.14	-
16	6.30	6.29	6.23	-	8.67	-	7.52	7.80	8.14	-	5.28	-	8.52	8.84	8.88
17	5.92	6.15	6.56	-	8.67	-	7.85	7.83	7.82	5.31	5.27	5.23	9.16	9.03	9.01

[a] Not included in the derivation of Eq. (9). [b] Not included in the derivation of Eq. (10).
[c] Not included in the derivation of Eq. (11). [d] Not included in the derivation of Eq. (12).
[e] Not included in the derivation of Eq. (13).

Table 3.14. Observed and calculated inhibition potencies of compounds of Table 3.10.

	log (1/IC_{50})														
	MMP-1			MMP-2			MMP-3			MMP-7			MMP-13		
Compd	Obsd	Calcd Eq. (9)	Loo	Obsd	Calcd Eq. (10)	Loo	Obsd	Calcd Eq. (11)	Loo	Obsd	Calcd Eq. (12)	Loo	Obsd	Calcd Eq. (13)	Loo
18	6.85	6.60	6.59	9.52	9.20	9.15	8.16[c]	7.60	-	-	5.91	-	-	8.60	
19	6.62	6.60	7.31	9.70	9.63	9.58	8.00	7.87	7.82	-	6.13	-	8.70	8.74	8.77
20	7.06	7.35	6.23	9.15	8.91	8.87	8.70	8.53	7.55	5.07[d]	5.63	-	9.00	9.04	9.05
21	6.58[a]	7.35	-	9.22	9.52	9.63	7.92[c]	8.46	-	-	6.02	-	9.30	9.24	9.21
22	6.85[a]	6.29	-	-	8.69	-	8.10	8.09	8.45	5.46	5.50	5.51	9.00	8.85	8.83
23	5.92	6.15	6.15	-	8.69	-	8.00	8.12	8.09	5.38	5.48	5.52	9.05	9.04	9.03
24	6.57[a]	6.15	-	-	8.87	-	8.10	7.94	8.15	5.77	5.59	5.52	9.10	9.09	9.09
25	6.36	6.15	6.17	-	8.97	-	8.00	7.84	7.91	5.62	5.66	5.68	9.05	9.13	9.14

[a-e] See foot notes of Table 3.13.

Table 3.15. Observed and calculated MMP inhibition potencies of compounds of Table 3.11.

	log ($1/IC_{50}$)														
	MMP-1			MMP-2			MMP-3			MMP-7			MMP-13		
Compd	Obsd	Calcd Eq. (14)	Loo	Obsd	Calcd Eq. (15)	Loo	Obsd	Calcd Eq. (16)	Loo	Obsd	Calcd Eq. (17)	Loo	Obsd	Calcd Eq. (18)	Loo
26	6.55	7.00	7.15	8.22	8.16	8.13	7.32[h]	8.06	-	5.13	5.23	5.32	9.00	9.17	9.22
27	6.68	6.39	6.32	-	8.21	-	8.05	8.07	8.07	6.21[i]	5.29	-	9.40	9.19	9.15
28	5.70[f]	9.40	7.66	-	8.12	-	7.92	8.07	8.07	5.01[i]	6.46	-	9.05	9.16	9.19
29	7.77	7.68	7.66	-	8.35	-	8.10	8.07	8.06	6.22	6.21	6.21	-	9.25	-
30	6.66	6.82	6.87	8.22	8.32	8.37	7.85	8.12	8.14	-	5.07	-	-	9.09	-
31	6.31	6.21	6.18	-	8.37	-	8.16	8.12	8.12	4.78	5.13	5.23	9.00	9.11	9.13
32	6.04	6.30	6.35	8.40	8.39	8.38	8.30	8.12	8.11	5.27	5.22	5.21	9.22	9.12	9.10
33	5.70[f]	9.22	-	-	8.28	-	7.92	8.12	8.14	5.13[i]	6.30	-	9.16	9.07	9.06
34	7.72	7.50	7.46	-	8.51	-	8.16	8.12	8.12	6.15	6.05	6.02	-	9.17	-
35	6.52	6.17	5.84	-	8.07	-	7.64	7.83	7.89	5.15	5.36	5.60	9.00	9.03	9.06
36	-	5.65	-	8.15	8.14	8.11	7.92	7.83	7.80	5.47	5.51	5.56	9.05	9.06	9.07
37	6.51	6.48	6.47	-	8.29	-	8.10	8.13	8.14	5.06	4.99	4.96	9.00	9.05	9.06
38	7.70	7.85	7.91	-	8.54	-	8.40	8.13	8.11	6.07	6.20	6.16	-	9.15	-
39	7.72	7.78	7.79	-	8.43	-	8.30	8.13	8.12	6.10	5.91	5.87	-	9.10	-
40	7.38	7.18	7.06	-	8.36	-	7.89	7.92	7.92	5.85	5.74	5.70	9.40	9.32	9.30
41	7.00	6.57	6.47	-	8.41	-	8.10	7.92	7.89	6.08	5.80	5.75	-	9.33	-
42	6.64	6.66	6.66	-	8.43	-	7.89	7.92	7.92	6.17	5.89	5.84	-	9.34	-

[f] Not included in the derivation of Eq. (14). [g] Not included in the derivation of Eq. (15).
[h] Not included in the derivation of Eq. (16). [i] Not included in the derivation of Eq. (17).
[j] Not included in the derivation of Eq. (18).

Table 3.16. Observed and calculated inhibition potencies of compounds of Table 3.12.

	log (1/IC$_{50}$)														
	MMP-1			MMP-2			MMP-3			MMP-7			MMP-13		
Compd	Obsd	Calcd Eq. (14)	Loo	Obsd	Calcd Eq. (15)	Loo	Obsd	Calcd Eq. (16)	Loo	Obsd	Calcd Eq. (17)	Loo	Obsd	Calcd Eq. (18)	Loo
43	6.70	6.76	6.78	-	8.84	-	8.10	8.12	8.13	5.75	5.54	5.42	9.30	9.30	9.30
44	6.24	5.88	5.84	-	8.87	-	7.48[h]	8.12	-	5.13	5.36	5.41	8.40[j]	9.31	-
45	6.59[f]	5.81	-	-	8.89	-	8.05	8.12	8.13	5.59	5.38	5.33	9.52	9.32	9.27
46	6.04	6.24	6.26	-	8.91	-	8.70[h]	8.12	-	5.80	5.69	5.67	9.52	9.33	9.28
47	6.52	6.85	6.90	-	8.92	-	8.52[h]	8.12	-	5.64	6.02	6.06	8.55[j]	9.33	-
48	5.75	5.94	5.96	9.00	8.96	8.94	7.59	7.56	7.55	5.04	4.73	4.50	8.36	8.47	8.57
49	7.68	7.44	7.35	-	9.03	-	8.22	8.12	8.12	6.51	6.52	6.52	-	9.37	-
50	6.22[f]	6.85	-	-	9.05	-	7.96	8.12	8.14	5.13[i]	6.30	-	9.15	9.38	9.47
51	6.13	6.40	6.43	7.31[g]	8.55	-	7.38[h]	7.93	-	6.07	5.99	5.98	-	9.40	-
52	6.11	6.27	6.29	8.70	8.76	8.77	8.52[h]	8.04	-	6.35	5.97	5.92	-	9.46	-
53	6.46[f]	5.94	-	9.10	8.82	8.75	7.96	8.03	8.03	5.59	5.98	6.04	9.40	9.49	9.52
54	6.32	6.02	5.99	-	8.83	-	8.16	8.03	8.03	6.00	6.07	6.08	9.40	9.50	9.53
55	5.54	5.73	5.77	8.70	8.88	8.94	7.34	7.47	7.54	4.96	5.10	5.18	8.70	8.65	8.62
56	6.24	6.12	6.10	9.40[g]	8.72	-	8.00	7.98	7.98	5.92	6.10	6.12	9.52	9.49	9.49
57	5.60	5.82	5.85	8.70	8.77	8.79	7.52	7.42	7.36	4.96	5.13	5.24	8.70	8.64	8.60

[f-j] See foot notes of Table 3.15.

Table 3.16. Observed and calculated inhibition potencies of compounds of Table 3.12.

	log (1/IC$_{50}$)														
	MMP-1			MMP-2			MMP-3			MMP-7			MMP-13		
Compd	Obsd	Calcd Eq. (14)	Loo	Obsd	Calcd Eq. (15)	Loo	Obsd	Calcd Eq. (16)	Loo	Obsd	Calcd Eq. (17)	Loo	Obsd	Calcd Eq. (18)	Loo
43	6.70	6.76	6.78	-	8.84	-	8.10	8.12	8.13	5.75	5.54	5.42	9.30	9.30	9.30
44	6.24	5.88	5.84	-	8.87	-	7.48[h]	8.12	-	5.13	5.36	5.41	8.40[j]	9.31	-
45	6.59[f]	5.81	-	-	8.89	-	8.05	8.12	8.13	5.59	5.38	5.33	9.52	9.32	9.27
46	6.04	6.24	6.26	-	8.91	-	8.70[h]	8.12	-	5.80	5.69	5.67	9.52	9.33	9.28
47	6.52	6.85	6.90	-	8.92	-	8.52[h]	8.12	-	5.64	6.02	6.06	8.55[j]	9.33	-
48	5.75	5.94	5.96	9.00	8.96	8.94	7.59	7.56	7.55	5.04	4.73	4.50	8.36	8.47	8.57
49	7.68	7.44	7.35	-	9.03	-	8.22	8.12	8.12	6.51	6.52	6.52	-	9.37	-
50	6.22[f]	6.85	-	-	9.05	-	7.96	8.12	8.14	5.13[i]	6.30	-	9.15	9.38	9.47
51	6.13	6.40	6.43	7.31[g]	8.55	-	7.38[h]	7.93	-	6.07	5.99	5.98	-	9.40	-
52	6.11	6.27	6.29	8.70	8.76	8.77	8.52[h]	8.04	-	6.35	5.97	5.92	-	9.46	-
53	6.46[f]	5.94	-	9.10	8.82	8.75	7.96	8.03	8.03	5.59	5.98	6.04	9.40	9.49	9.52
54	6.32	6.02	5.99	-	8.83	-	8.16	8.03	8.03	6.00	6.07	6.08	9.40	9.50	9.53
55	5.54	5.73	5.77	8.70	8.88	8.94	7.34	7.47	7.54	4.96	5.10	5.18	8.70	8.65	8.62
56	6.24	6.12	6.10	9.40[g]	8.72	-	8.00	7.98	7.98	5.92	6.10	6.12	9.52	9.49	9.49
57	5.60	5.82	5.85	8.70	8.77	8.79	7.52	7.42	7.36	4.96	5.13	5.24	8.70	8.64	8.60

[f-j] See foot notes of Table 3.15.

MMP-1

$$\log (1/IC_{50}) = 6.775\ (\pm 0.268) - 0.286\ (\pm 0.166)\,{}^{1}\chi^{v}_{R} + 0.748(\pm 0.309)I_{W}$$

$$n = 19,\ r = 0.901,\ r^{2}_{cv} = 0.63,\ s = 0.23,\ F_{2,16} = 34.71(6.23) \qquad (9)$$

MMP-2

$$\log (1/IC_{50}) = 8.369(\pm 0.414) + 0.202(\pm 0.106)\,{}^{1}\chi^{v}_{N}$$

$$n = 9,\ r = 0.863,\ r^{2}_{cv} = 0.56,\ s = 0.23,\ F_{1,17} = 20.46(8.40) \qquad (10)$$

MMP-3

$$\log (1/IC_{50}) = -0.501(\pm 0.206)\,{}^{1}\chi^{v}_{N} + 0.050(\pm 0.029)({}^{1}\chi^{v}_{N})^{2} + 0.656(\pm 0.218)I_{W} - 2.946(\pm 0.945)S_{S} - 7.850(\pm 5.066)$$

$$n = 20,\ r = 0.916,\ r^{2}_{cv} = 0.65,\ s = 0.18,\ F_{4,15} = 19.58(4.89),\ ({}^{1}\chi^{v}_{N})_{opt} = 5.01 \qquad (11)$$

MMP-7

$$\log (1/IC_{50}) = 0.175(\pm 0.084)\,{}^{1}\chi^{v}_{N} + 1.863(\pm 0.982)S_{S} + 0.405(\pm 0.234)I_{W} + 15.319(\pm 5.224)$$

$$n = 12,\ r = 0.866,\ r^{2}_{cv} = 0.47,\ s = 0.10,\ F_{3,8} = 8.01(7.59) \qquad (12)$$

MMP-13

$$\log (1/IC_{50}) = 8.098(\pm 0.269) + 0.065(\pm 0.054)\,{}^{1}\chi^{v}_{N} + 0.379(\pm 0.124)\,{}^{1}\chi^{v}_{R} + 0.535(\pm 0.211)I_{W}$$

$$n = 18,\ r = 0.900,\ r^{2}_{cv} = 0.72,\ s = 0.15,\ F_{3,14} = 19.87(5.56) \qquad (13)$$

In these correlations, an indicator variable I_W has been used for W substituent. If W = H, $I_W = 0$, otherwise $I_W = 1$. Now the presence of I_W with positive coefficient in all the equations, except in Eq. (10), suggests that the presence of a substituent at the amide nitrogen would be beneficial to the activity. It is also to be noted that in all the equations I_W has almost equal weightage indicating that all the enzymes, except MMP-2, might have identical active site to accommodate the W-substituent. However, the whole amide group does not appear to behave identically with all the enzymes. In MMP-2, MMP-7 and MMP-13 (Eqs. (10), (12) and (13)), its connectivity index (${}^{1}\chi^{v}_{N}$) appears to have

always a positive effect on the inhibition, but in MMP-3 (Eq. (11)), its initial effect is detrimental till it attains a value of 5.01, which is quite high. Thus a large amide group does not seem to be preferred by MMP-3. In MMP-1, it was not found to have any effect (Eq. (9)). As far as the substituent R at the phenyl ring is concerned, its connectivity index $^{1}\chi^{v}_{R}$ is found to produce a detrimental effect on the inhibition of MMP-1 (Eq. (9)) but a beneficial effect on MMP-13 inhibition (Eq. (13)). On the inhibition of other enzymes, $^{1}\chi^{v}_{R}$ was found to have no effect.

An E-state index S_S is found to be important only in the case of MMP-3 and MMP-7 inhibitions (Eqs. (11) and (12)), but its coefficients have sign opposite to each other in these two cases. The S_S refers to the availability of π or lone pair electrons on the sulfur atom. Its negative coefficient in Eq. (11) suggests that an increase in the value of S_S would decrease the activity. One may assume that sulfur atom might be facing some negatively charged site in MMP-3, thus undergoing a charge-charge repulsive interaction. However, its positive coefficient in Eq. (12) leads to assume that in the case of MMP-7 it may not be sulfur atom but the two oxygen atoms attached to it that might have the opportunity to form the hydrogen bonds with the receptor. It has been pointed out in many studies that SO_2 of the inhibitor may be involved in strong hydrogen bonding with amino acid residues from the active site cleft of the enzyme. In SO_2, sulfur itself may not participate in the hydrogen bondings, but it can enhance the participation of the two oxygen atoms by donating them a major share of the lone pairs of electrons, now forming the coordinate bonds. This leads to the development of partial negative charges on the oxygen atoms, to the extent they attract the lone pairs of sulfur, and this makes them capable of forming the hydrogen bonds. The strength of hydrogen bonds will depend on the partial negative charges developed on them. An attempt was made to account for the effect of an SO_2 group vis-a-vis a carbonyl group present in the Q moiety of the amide group, but nothing specific came out.

A similar correlation analysis was performed on the two series as listed in Tables 3.11 and 3.12. In these series the amide moiety forms a cyclic structure that has a carbonyl group on both sides of the nitrogen in series of Table 3.12 but not in the series

of Table 3.11. For a combine of Tables 3.11 and 3.12, the following correlations were obtained with the use of activity data as given in Tables 3.15 and 3.16.

MMP-1

$$\log(1/IC_{50}) = -4.721(\pm1.093)^{1}\chi^{v}_{R} + 1.858(\pm0.387)(^{1}\chi^{v}_{R})^{2} + 5.678(\pm2.511)S_S + 1.444(\pm0.712)I_Y + 42.213(\pm14.811)$$

$n = 26,\ r = 0.933,\ r^2_{cv} = 0.78,\ s = 0.27,\ F_{4,21} = 35.36(4.37)$ (14)

MMP-2

$$\log(1/IC_{50}) = -1.965\ (\pm0.823)\ S_S - 0.217(\pm0.195)^{1}\chi^{v}_{N} - 2.195(\pm4.679)$$

$n = 9,\ r = 0.926,\ r^2_{cv} = 0.76,\ s = 0.15,\ F_{2,6} = 18.18(10.92)$ (15)

MMP-3

$$\log(1/IC_{50}) = 7.864(\pm0.278) - 0.137(\pm0.080)^{1}\chi^{v}_{N} + 0.561(\pm0.177)I_R$$

$n = 26,\ r = 0.843,\ r^2_{cv} = 0.63, s = 0.14,\ F_{2,23} = 28.27(5.66)$ (16)

MMP-7

$$\log(1/IC_{50}) = 1.843(\pm1.541)^{1}\chi^{v}_{N} - 0.274(\pm0.247)(^{1}\chi^{v}_{N})^{2} - 1.709(\pm1.025)1\chi^{v}_{R} + 0.743(\pm0.348)(^{1}\chi^{v}_{R})^{2} - 1.811(\pm0.931)S_S + 0.928(\pm0.346)I_R - 7.950(\pm5.200)$$

$n = 27,\ r = 0.903,\ r^2_{cv} = 0.68,\ s = 0.25,\ F_{6,20} = 14.71(3.87),\ (^{1}\chi^{v}_{N})_{opt} = 3.363$ (17)

MMP-13

$$\log(1/IC_{50}) = 1.158(\pm0.964)^{1}\chi^{v}_{N} - 0.187(\pm0.151)(^{1}\chi^{v}_{N})^{2} - 0.799(\pm0.487)S_S + 0.871(\pm0.213)I_R + 2.102(\pm3.042)$$

$n = 20,\ r = 0.915,\ r^2_{cv} = 0.73,\ s = 0.14,\ F_{4,15} = 19.38(4.89),\ (^{1}\chi^{v}_{N})_{opt} = 3.096$ (18)

From these correlations, the E-state index S_S is found to be important in the inhibition of all the enzymes except the MMP-3. Its positive coefficient in MMP-1 (Eq. (14)) suggests, as already discussed in connection to Eq. (12), a possible involvement of oxygen atoms of SO_2 group in the hydrogen bonding with the receptor. In other cases, its negative coefficient indicates the charge-charge repulsive interaction of the sulfur atom

with the receptors. The cyclic amide groups in these series appears to have predominantly detrimental effect either for all values of $^{1}\chi^{v}_{N}$ as in MMP-2 (Eq. (15)) and MMP-3 (Eq. (16)) or after an optimum value of $^{1}\chi^{v}_{N}$ as in MMP-7 (Eq. (17)) and MMP-13 (Eq. (18)). For both MMP-7 and MMP-13, the $(^{1}\chi^{v}_{N})_{opt}$ is almost same, i.e. 3.363 and 3.096, respectively. This detrimental effect of amide groups may be due to their steric roles. The MMP-1 inhibition, however, was not found to be affected by the amide groups. This was also the case for MMP-1 inhibition in the series of Tables 3.9 and 3.10.

As far the effect of phenyl ring substituents R is concerned, they are again found to have negative effect on MMP-1 and MMP-7 (Eq. (14)) and (Eq. (17)) but only to an optimum value of $^{1}\chi^{v}_{R}$ equal to 1.270 and 1.150, respectively, beyond which they may be beneficial. Both values are essentially identical. In deriving Eqs. (14-18) some indicator parameters have also been used. In Eq. (14), I_Y is equal to zero for $Y=CH_2$ and unity for $Y=SO_2$ or CO and I_R in Eqs. (16-18) is for R-substituents. It has been given a value of one for all R substituents except R = $OCH_2CH_2OCH_3$ for which it is zero. Now its positive coefficient in all three equations suggests that except a substituent of the type $OCH_2CH_2OCH_3$ all other R-substituents at the phenyl ring would be beneficial to the inhibition potency of the compounds against MMP-3, MMP-7 and MMP-13. $OCH_2CH_2OCH_3$ is a lengthy substituent as compared to others and hence its disadvantageous role can be attributed to its length. All other substituents, which are mainly alkoxy groups have their $^{1}\chi^{v}_{R}$ value higher enough than the optimum value of $^{1}\chi^{v}_{R}$ (1.150-1.270) to be advantageous to the activity. The only exception is OCH_3 group.

The variable I_Y in Eq. (14) has the positive coefficient suggesting that SO_2 or CO moiety adjacent to nitrogen in amide group may be preferred to a CH_2 moiety. These groups may probably form the hydrogen bonds with the receptor. In deriving some of the equations, a few outliers were excluded as given in the footnotes of Tables 3.13 – 3.14 and 3.15 – 3.16. No specific reasons could be found for the aberrant behaviors of these outliers.

3.3 Anthranilic Hydroxamic Acid Inhibitors

Levin et al. [18-21] recently reported four different series of anthranic hydroxamic acid-based MMP inhibitors (Figure 3.3) which are listed in Tables 3.17 – 3.20, respectively, along with the physicochemical parameters that were found to be correlated with their MMP inhibition potencies. Their inhibition potencies – observed ones as well as those calculated from the correlations obtained – are listed in Tables 3.21 – 3.24, respectively. The most relevant physicochemical parameter that has been found to be relevant in most of the cases is hydrophobic parameter, ClogP, of the molecules. Many other parameters were also calculated and used but they were rarely found of any use. However, many indicator variables were used that described the specific roles of some structural features present in the molecules. These parameters are defined as and when they appear in the correlations.

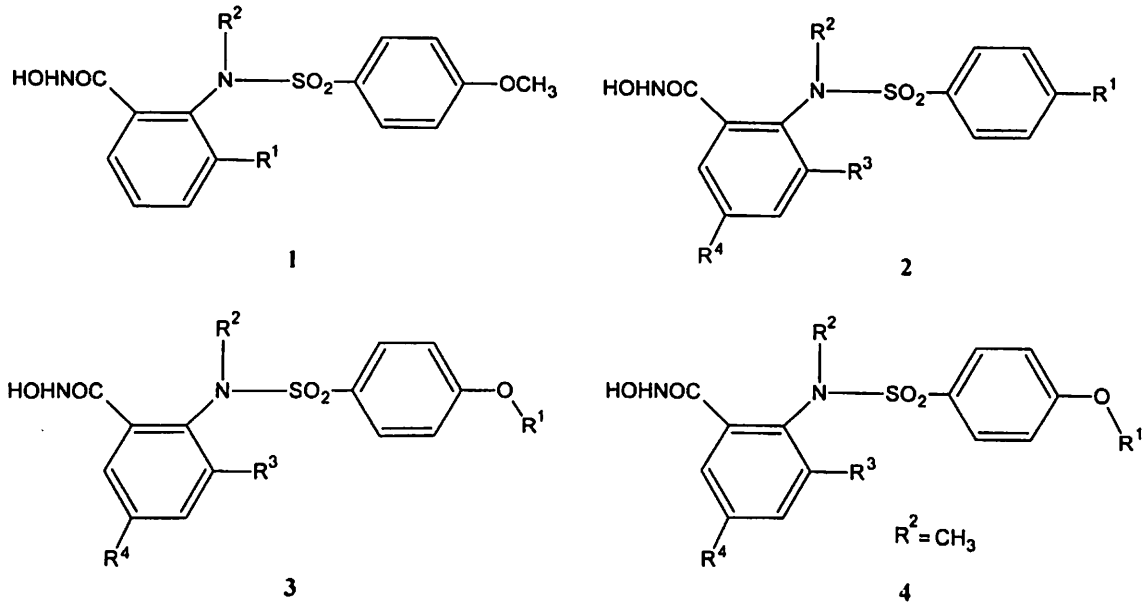
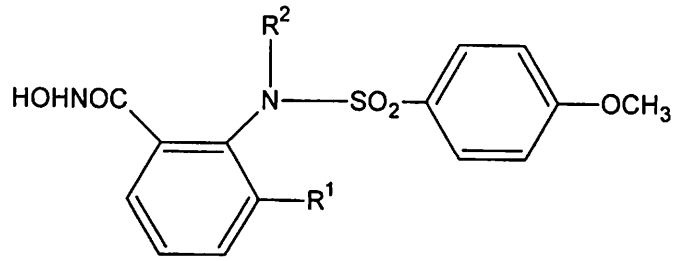


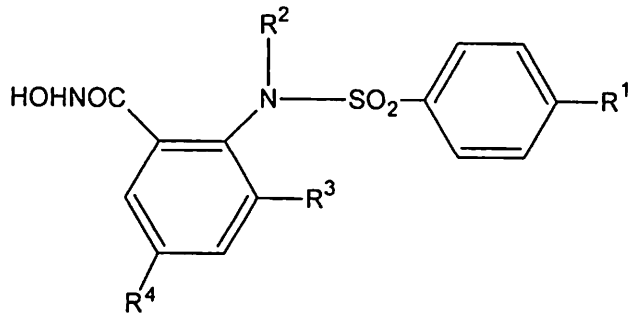
Figure 3.3. A series of anthranilic hydroxamic acid derivatives

Table 3.17. Analogs of **1** and their related physicochemical parameters.



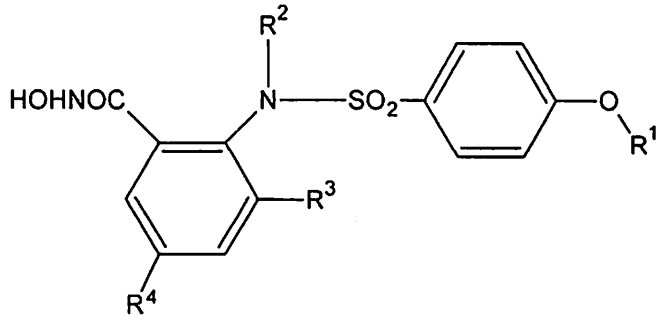
Compd	R^1	R^2	ClogP
1	H	CH_2Ph	1.681
2	CH_3	CH_2Ph	1.840
3	CH_3	CH_2-3-Py	0.343
4	OCH_3	CH_2Ph	1.711
5	Cl	CH_2Ph	1.784
6	NO_2	CH_2Ph	0.939
7	$N(CH_3)_2$	CH_2Ph	1.905
8	CF_3	CH_2Ph	1.670
9	$OCH_2CONHOH$	CH_2Ph	-0.120
10	$OC(CH_3)_2CONHOH$	CH_2Ph	0.498
11	CO_2CH_3	CH_2-3-Py	0.187

Table 3.18. Analogs of **2** and their related physicochemical parameters.



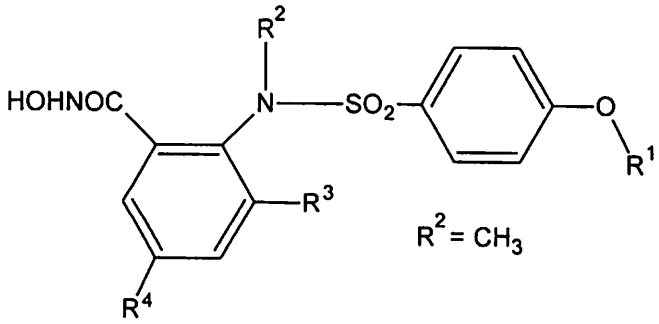
Compd	R^1	R^2	R^3	R^4	ClogP	I_1	I_2	I_3	I_4	$I_{4,Br}$
1	OCH_3	CH_2-3-Py	CH_3	H	0.343	0	1	0	0	0
2	OCH_3	CH_2-3-Py	CH_3	Br	1.426	0	1	0	0	1
3	OCH_3	CH_2-3-Py	CH_3	CH_3	0.842	0	1	0	0	0
4	OCH_3	CH_2-3-Py	CH_3	Ph	2.231	0	1	0	1	0
5	OCH_3	CH_2-3-Py	CH_3	Ph-4-CF_3	3.191	0	1	0	1	0
6	OCH_3	CH_2-3-Py	CH_3	2-Naphthyl	3.405	0	1	0	1	0
7	OCH_3	CH_2-Ph	CH_3	CH_2NEt_2	2.732	0	0	0	0	0
8	OCH_3	CH_2-3-Py	CH_3	$N(CH_3)_2$	0.567	0	1	0	0	0
9	OCH_3	CH_2-3-Py	Ph	CH_3	2.111	0	1	1	0	0
10	OCH_3	CH_2-3-Py	2-Furyl	CH_3	0.285	0	1	1	0	0
11	OEt	CH_2-Ph	CH_3	CH_3	2.868	0	0	0	0	0
12	O-*n*-Bu	CH_2-Ph	CH_3	CH_3	3.926	0	0	0	0	0
13	OCH_2Ph	CH_2-Ph	CH_3	CH_3	4.107	1	0	0	0	0
14	$O(CH_2)_2Ph$	CH_2-Ph	CH_3	CH_3	4.436	0	0	0	0	0
15	OPh	CH_2-Ph	CH_3	CH_3	4.268	0	0	0	0	0
16	OPh-4-*t*Bu	CH_3	CH_3	Br	4.910	0	0	0	0	1
17	O-4-Py	CH_3	CH_3	H	0.504	0	0	0	0	0
18	O-4-Py	CH_3	H	H	0.345	0	0	0	0	0
19	SPh	CH_3	CH_3	CH_3	2.840	0	0	0	0	0
20	OPh-4-OCH_3	CH_2-3-Py	CH_3	H	2.031	0	1	0	0	0
21	Ph-3,4-(-OCH_2O-)	CH_2-3-Py	CH_3	H	2.050	0	1	0	0	0
22	OCH_2Ph	CH_2-Ph	CH_3	Br	3.194	1	0	0	0	1
23	OCH_2Ph	CH_3	CH_3	Br	3.452	1	0	0	0	1
24	OCH_2-3-Thienyl	CH_3	CH_3	Br	3.098	0	0	0	0	1
25	OCH_2-2-Thiazolyl	CH_3	CH_3	Br	1.796	0	0	0	0	1
26	OCH_2-3-Py	CH_3	CH_3	Br	1.955	0	0	0	0	1

Table 3.19. Analogs of **3** and their related physicochemical parameters.



Compd	R^1	R^2	R^3	R^4	ClogP	Pol	I_1	I_2	I_3	$I_{4D\alpha}$
1	CH_3	CH_2-3-Py	CH_3	H	0.343	4.450	0	1	0	0
2	CH_3	CH_2-3-Py	CH_3	Br	1.426	4.750	0	1	0	1
3	CH_3	CH_2-Ph-4-Cl	CH_3	H	2.553	4.730	0	1	0	0
4	CH_3	CH_2Ph-4-O$(CH_2)_2NC_5H_{10}$	CH_3	H	3.092	5.960	0	1	0	0
5	CH_3	CH_2Ph-4-O$(CH_2)_2NC_5H_{10}$	CH_3	Br	4.175	6.270	0	1	0	1
6	CH_3	CH_2Ph-4-$CH_2N(CH_3)_2$	CH_3	H	1.674	5.240	0	1	0	0
7	CH_3	CH_2Ph-4-N$[(CH_2)_2]_2NCH_3$	CH_3	H	1.738	5.680	0	1	0	0
8	CH_3	$CH_2CCCH_2NEt_2$	CH_3	H	1.954	4.920	0	1	0	0
9	CH_3	$CH_2CCCH_2NEt_2$	CH_3	Br	3.037	5.220	0	1	0	1
10	CH_3	$CH_2CCCH_2N[(CH_2)_2]_2NCH_3$	CH_3	Br	1.199	5.480	0	1	0	1
11	CH_3	CH_3	CH_2NEt_2	H	0.465	4.440	0	0	0	0
12	CH_3	CH_3	$CH_2N[(CH_2)_2]_2O$	H	-0.680	4.430	0	0	0	0
13	CH_3	CH_3	CH_2ProCH$_3$	H	-0.002	4.800	0	0	0	0
14	CH_3	CH_3	CH_2Im	H	-0.814	4.320	0	0	0	0
15	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	H	-0.238	4.700	0	0	1	0
16	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	Br	0.845	5.000	0	0	1	1
17	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NPh$	Br	2.395	5.800	0	0	0	1
18	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NBoc$	Br	2.376	5.820	0	0	0	1
19	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	Ph-4-OCF_3	2.714	5.950	0	0	1	0
20	CH_3	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	2-Naphthyl	2.824	6.380	0	0	1	0
21	Ph-4-Cl	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	H	2.523	5.690	1	0	1	0
22	Ph-4-Cl	CH_3	$CH_2N[(CH_2)_2]_2NCH_3$	Br	3.606	5.990	1	0	1	1

Table 3.20. Analogs of **4** and their related physicochemical parameters.



Compd	R^1	R^3	R^4	ClogP	Pol	$I_{1,CC}$	$I_{1,N}$	$I_{4,Br}$
1	CH_3	CH_3	Br	1.155	3.860	0	0	1
2	CH_3	$CH_2[(CH_2)_2]_2NCH_3$	Br	0.833	4.850	0	0	1
3	CH_2-3-C_5H_4N	CH_3	Br	1.426	4.750	0	0	1
4	$(CH_2)_3CH_3$	CH_3	Br	2.722	4.410	0	0	1
5	CH_2CCH	CH_3	Br	1.755	4.140	1	0	1
6	$CH(CH_3)CCH$	CH_3	Br	2.064	4.330	1	0	1
7	CH_2CCCH_3	CH_3	Br	2.284	4.330	1	0	1
8	$CH_2CCCH_2CH_3$	CH_3	Br	2.284	4.520	1	0	1
9	$CH_2CC(CH_2)_2CH3$	CH_3	Br	3.342	4.700	1	0	1
10	$CH_2CC(CH_2)_3CH3$	CH_3	Br	3.871	4.890	1	0	1
11	CH_2CCPh	CH_3	Br	2.873	5.130	1	0	1
12	CH_2CCCH_2OH	CH_3	Br	1.197	4.400	1	0	1
13	$CH_2CCCH_2OCH_3$	CH_3	Br	1.913	4.590	1	0	1
14	$CH_2CCCH_2NHCH_3$	CH_3	Br	1.443	4.660	1	1	1
15	$CH_2CCCH_2NH(CH_2)_3N(CH_3)_2$	CH_3	Br	2.200	5.550	1	1	1
16	$CH_2CCCH_2N(CH_2CH_3)_2$	CH_3	Br	3.037	5.220	1	1	1
17	CH_2CCCH_3	CH_3	H	1.201	4.030	1	0	0
18	CH_2CCCH_3	H	H	1.042	3.850	1	0	0
19	CH_2CCCH_3	$CH_2[(CH_2)_2]_2NCH_3$	Br	1.686	5.130	1	0	1
20	CH_2CCCH_3	$CH_2[(CH_2)_2]_2NCH_3$	Ph	2.491	5.810	1	0	0

Table 3.21. Observed and calculated MMP inhibition potencies of compounds of Table 3.17. Observed activities have been taken from ref. [18].

Compd	log ($1/IC_{50}$)								
	MMP-1			MMP-9			MMP-13		
	Obsd	Calcd Eq. 19	Loo	Obsd	Calcd Eq. 20	Loo	Obsd	Calcd Eq. 21	Loo
1	6.19	6.24	6.25	6.19[b]	7.56	-	6.26	6.61	6.71
2	6.94[a]	6.45	-	7.64	7.47	7.42	7.30[c]	6.42	-
3	6.84	6.57	6.43	8.30	8.33	8.34	8.10	8.27	8.32
4	6.28	6.27	6.27	7.64	7.54	7.52	6.86	6.58	6.50
5	6.40	6.37	6.35	7.51	7.50	7.49	-	6.49	-
6	6.69	5.93	-	7.89	7.97	8.00	7.38	7.53	7.55
7	-	6.56	-	7.19	7.43	7.50	6.27	6.34	6.36
8	-	6.22	-	7.57	7.56	7.56	6.87	6.63	6.56
9	7.62	7.60	7.45	8.70	8.61	8.54	9.00	8.85	8.76
10	6.22[a]	6.33	6.44	8.40	8.23	8.21	8.22	8.08	8.06
11	6.68	6.87	6.93	8.22	8.42	8.48	8.40	8.47	8.49

[a]Not included in the derivation of Eq. 19.
[b]Not included in the derivation of Eq. 20.
[c]Not included in the derivation of Eq. 21.

Table 3.22. Observed and calculated MMP inhibition potencies of compounds of Table 3.18. Observed activities have been taken from ref. [19].

	log ($1/IC_{50}$)											
	MMP-1			MMP-9			MMP-13			TACE		
Compd	Obsd	Calcd Eq. 22	Loo	Obsd	Calcd Eq. 23	Loo	Obsd	Calcd Eq. 24	Loo	Obsd	Calcd Eq. 25	Loo
1	6.84	6.93	6.97	8.30	8.25	8.23	8.10	7.84	7.79	6.64	7.10	7.28
2	6.91	6.73	6.70	7.62	7.96	7.99	7.70	7.64	7.63	7.37	7.56	7.62
3	6.88	6.84	6.83	7.82	8.11	8.16	7.96	7.75	7.72	7.15	7.02	6.99
4	6.71	6.57	6.56	8.52	8.93	9.15	8.40	8.83	9.06	7.19	6.79	6.75
5	6.27	6.39	6.40	9.00	8.67	8.51	8.70	8.65	8.63	6.53	6.64	6.65
6	6.13	6.35	6.38	8.70	8.62	8.58	9.00	8.61	8.42	6.71	6.60	6.59
7	5.98	6.48	6.53	8.30	7.61	7.55	6.95	7.40	7.44	-	6.71	-
8	7.13	6.89	6.82	8.70	8.19	8.09	7.41	7.80	7.86	6.20[d]	7.06	-
9	6.99	7.19	7.42	8.15	7.78	7.75	8.52	8.59	8.63	6.88	6.81	6.80
10	7.74	7.54	7.31	8.10	8.26	8.30	9.00	8.93	8.85	7.21	7.11	7.07
11	6.54	6.45	6.44	-	7.58	-	7.62	7.37	7.35	6.76	6.69	6.68
12	-	5.23	-	6.84	7.30	7.39	6.86	7.18	7.24	6.42	6.52	6.53
13	-	5.19	-	6.26	6.01	5.88	6.02	6.09	6.13	6.37	6.49	6.51
14	6.13	6.15	6.15	7.34[b]	7.16	-	7.12	7.08	7.07	6.33	6.43	6.46
15	6.42	6.18	6.11	8.40	7.16	7.11	8.22[c]	6.04	-	-	6.46	-
16	-	5.04	-	6.90	7.04	7.10	7.36	7.00	6.85	-	6.99	-
17	5.49	5.88	6.18	8.15[b]	8.20	-	8.40	7.81	7.91	-	7.07	-
18	-	5.91	-	6.82	8.20	8.21	7.42	7.84	7.92	-	7.10	-
19	5.88	5.43	5.19	8.10[b]	7.58	-	8.52[c]	6.30	-	6.14[d]	6.69	-
20	5.64[a]	6.61	-	6.82	7.59	7.53	7.74	7.53	7.51	-	6.82	-
21	-	6.61	-	-	7.79	-	7.59	7.52	7.52	-	6.82	-
22	-	5.37	-	5.46	6.25	6.65	5.76	6.26	6.52	6.55[d]	7.27	-
23	-	5.32	-	6.72[b]	7.42	-	6.79	6.21	5.93	7.24	7.23	7.22
24	5.33	5.38	5.41	6.63	6.18	5.91	6.85	7.33	7.38	7.25	7.29	7.30
25	-	5.63	-	6.02	7.52	7.62	6.18[c]	6.49	-	7.64	7.50	7.46
26	-	5.60	-	-	7.82	-	-	6.46	-	7.55	7.47	7.45

[a]Not included in the derivation of Eq. 22.
[b]Not included in the derivation of Eq. 23.
[c]Not included in the derivation of Eq. 24.
[d]Not included in the derivation of Eq. 25.

Table 3.23. Observed and calculated MMP inhibition potencies of compounds of Table 3.19. Observed activities have been taken from ref. [20].

	log (1/IC$_{50}$)											
	MMP-1			MMP-9			MMP-13			TACE		
Compd	Obsd	Calcd Eq. 27	Loo	Obsd	Calcd Eq. 28	Loo	Obsd	Calcd Eq. 29	Loo	Obsd	Calcd Eq. 26	Loo
1	6.84	6.78	6.76	8.30	8.10	8.07	8.10	7.78	7.73	6.64	6.73	6.74
2	6.48[a]	6.95	-	8.15	8.05	8.04	7.74	7.91	7.92	6.45[d]	7.39	-
3	6.41	6.64	6.70	8.10	8.17	8.18	7.74	7.90	7.91	6.19	6.51	6.57
4	6.75	6.61	6.56	8.15	8.28	8.30	7.25[c]	8.40	-	6.56	6.46	6.43
5	7.46[a]	6.78	-	8.70	8.61	8.46	8.52	8.53	8.53	6.97	7.11	7.16
6	6.67	6.70	6.70	8.52[b]	8.06	-	7.96	8.11	8.12	6.61	6.60	6.60
7	6.85	6.69	6.67	8.15	8.07	8.05	7.70[c]	8.29	-	6.84	6.59	6.57
8	6.33[a]	6.68	-	7.96	8.09	8.10	7.72	7.98	8.00	6.66	6.57	6.56
9	6.82	6.85	6.86	7.85[b]	8.27	-	8.15	8.10	8.09	7.44	7.23	7.19
10	6.89	6.96	7.00	8.00	8.05	8.06	8.22	8.21	8.20	7.59	7.41	7.37
11	6.13	6.14	6.15	8.10	8.09	8.08	7.08[c]	7.78	-	6.68	6.72	6.73
12	6.22	6.21	6.21	8.30	8.28	8.27	7.85	7.77	7.76	6.76	6.84	6.85
13	6.29	6.17	6.14	8.30	8.14	8.12	8.22	7.93	7.90	6.70	6.77	6.78
14	6.11	6.22	6.26	8.00	8.31	8.49	7.37	7.73	7.80	6.80	6.85	6.86
15	6.51	6.50	6.50	9.00	8.88	8.82	7.92	7.89	7.88	6.81	6.79	6.79
16	6.71	6.67	6.64	8.70	8.75	8.77	8.30	8.01	7.99	7.59	7.45	7.40
17	6.35	6.26	6.21	8.52[b]	8.14	-	8.52	8.34	8.31	7.06	7.29	7.33
18	6.17	6.26	6.30	8.15	8.14	8.14	8.22	8.34	8.36	7.20	7.29	7.31
19	6.13	6.32	6.43	8.70	8.89	8.93	8.40	8.40	8.40	6.68	6.50	6.46
20	6.46	6.31	6.22	8.70	8.91	8.96	8.52	8.57	8.59	7.31[d]	6.48	-
21	6.81	6.87	6.95	9.00	8.86	8.82	9.10	9.06	9.03	6.91[d]	6.51	-
22	7.09	7.03	6.96	9.30	9.11	9.02	9.15	9.19	9.22	7.10	7.17	7.18

[a]Not included in the derivation of Eq. 27.
[b]Not included in the derivation of Eq. 28.
[c]Not included in the derivation of Eq. 29.
[d]Not included in the derivation of Eq. 26.

Table 3.24. Observed and calculated MMP inhibition potencies of compounds of Table 3.20. Observed activities have been taken from ref. [21].

	log (1/IC_{50})											
	MMP-1			MMP-9			MMP-13			TACE		
Compd	Obsd	Calcd Eq. 33	Loo	Obsd	Calcd Eq. 30	Loo	Obsd	Calcd Eq. 31	Loo	Obsd	Calcd Eq. 32	Loo
1	6.94	6.59	6.41	7.96	7.86	7.78	7.68	7.85	7.94	7.49	7.56	7.58
2	6.71	6.78	6.85	8.70	8.35	8.11	8.30	7.95	7.73	7.59	7.65	7.67
3	-	6.43	-	-	8.31	-	-	7.76	-	7.55	7.48	7.46
4	5.60	5.65	5.66	7.68	8.13	8.36	7.17	7.35	7.50	7.17	7.11	7.08
5	6.95[a]	6.23	-	7.82[b]	6.91	-	7.28	6.77	6.70	7.96	7.88	7.87
6	5.81	6.05	6.08	6.34	6.29	6.27	6.36	6.67	6.70	6.91[d]	7.79	-
7	5.79	5.91	5.93	6.52	6.29	6.24	6.81	6.60	6.57	7.80	7.73	7.72
8	5.91	5.91	5.92	6.10	6.38	6.42	6.54	6.60	6.60	7.92	7.73	7.70
9	5.63	5.28	5.09	6.63	6.47	6.45	6.45	6.26	6.20	7.33	7.43	7.45
10	-	4.97	-	6.41	6.57	6.59	6.15	6.09	6.05	7.47	7.28	7.18
11	5.42	5.56	5.60	6.07	6.69	6.79	6.49	6.41	6.40	7.18	7.56	7.62
12	5.49[a]	6.56	-	6.32	6.32	6.32	7.08	6.95	6.91	8.15	8.04	8.00
13	5.11[a]	6.14	-	6.41	6.42	6.42	6.63	6.72	6.73	7.96	7.83	7.81
14	-	6.42	-	6.19	5.64	5.25	6.59	6.33	6.17	7.24	7.08	6.87
15	-	5.96	-	5.92	6.09	6.20	6.04	6.09	6.12	7.54[d]	6.86	-
16	-	5.47	-	5.55	5.93	6.12	5.62	5.82	5.96	6.46	6.62	6.83
17	-	6.56	-	-	6.14	-	6.38	6.94	7.08	7.55	7.61	7.64
18	-	6.65	-	-	6.05	-	-	7.00	-	7.57	7.65	7.70
19	5.78[a]	6.27	-	6.78	6.69	6.67	6.60	6.79	6.81	7.60	7.90	7.95
20	5.72	5.79	5.80	7.55	7.03	6.57	7.33[c]	6.53	-	7.38	7.24	7.14

[a]Not included in the derivation of Eq. 33.
[b]Not included in the derivation of Eq. 30.
[c]Not included in the derivation of Eq. 31.
[d]Not included in the derivation of Eq. 32.

For the compounds of Table 3.17, the excellent correlations were obtained between the inhibition potencies against all the three MMPs, MMP-1, MMP-9 and MMP-13, and the hydrophobicity of the molecule (Eqs. 19-21).

MMP-1

$\log (1/IC_{50}) = 7.286(\pm0.331) - 2.473(\pm1.279)ClogP + 1.098(\pm0.683)(ClogP)^2$

$n = 7, r = 0.960, r^2_{cv} = 0.80, s = 0.18, F_{1,4} = 23.53(21.20), ClogP_o = 1.13$ (19)

MMP-9

$\log (1/IC_{50}) = 8.525(\pm0.193) - 0.576(\pm0.147)ClogP$

$n = 10, r = 0.954, r^2_{cv} = 0.86, s = 0.15, F_{1,8} = 81.56(11.26)$ (20)

MMP-13

$\log (1/IC_{50}) = 8.699(\pm0.302) - 1.240(\pm0.247)ClogP$

$n = 9, r = 0.976, r^2_{cv} = 0.92, s = 0.23, F_{1,7} = 140.93(12.25)$ (21)

The correlations expressed by Eqs. 19-21 exhibit that highly hydrophobic molecules will not be favored. It therefore suggests that probably MMPs do not possess hydrophobic sites to interact with the molecules. The high r^2_{cv} value (> 0.60) in each equation suggests that each equation is quite significant and has very high predictive value. Tables also give the predicted values from leave-one-out equations that are in very much agreement to the observed values.

For the compounds of Table 3.18 also, we could not find any positive role of the lipophilicity of the molecules (Eqs. 22–25). However, some specific substituents were found to be favorable to the activity as indicated by some indicator parameters. The indicator parameters used are I_1, I_2, I_3, I_4, and $I_{4,Br}$.

MMP-1

$\log (1/IC_{50}) = 1.020(\pm0.396)I_2 + 0.596(\pm0.487)I_3 - 0.192(\pm0.118)ClogP + 5.979(\pm0.432)$

$n = 16, r = 0.919, r^2_{cv} = 0.67, s = 0.28, F_{3,12} = 21.86(5.95)$ (22)

MMP-9

$$\log (1/IC_{50}) = 8.336(\pm0.492) - 0.265(\pm0.183)ClogP - 1.241(\pm0.725)I_1 + 1.183(\pm0.691)I_4$$

$$n = 19,\ r = 0.882,\ r^2_{cv} = 0.64,\ s = 0.50,\ F_{3,15} = 17.47(5.42) \qquad (23)$$

MMP-13

$$\log (1/IC_{50}) = 7.902(\pm0.366) - 0.184(\pm0.138)ClogP - 1.051(\pm0.552)I_1 + 1.079(\pm0.626)I_3 + 1.341(\pm0.527)I_4$$

$$n = 22,\ r = 0.919,\ r^2_{cv} = 0.75,\ s = 0.38,\ F_{4,17} = 23.06(4.67) \qquad (24)$$

TACE

$$\log (1/IC_{50}) = 0.637(\pm0.229)I_{4,Br} - 0.163(\pm0.084)ClogP + 7.156(\pm0.248)$$

$$n = 16,\ r = 0.898,\ r^2_{cv} = 0.69,\ s = 0.20,\ F_{2,13} = 27.14(6.70) \qquad (25)$$

I_1 stands for R^1-substituents and has a value of unity for $R^1 = OCH_2Ph$ and zero for others, I_2 stands for R^2-substituents and has a values of unity for $R^2 = CH_2$-3-pyridyl group and zero for others, I_3 stands for R^3-substiutents and is equal to 1 for R^3 = an aromatic substituent and zero otherwise, similarly I_4 that stands for R^4 –substituents also has a value of unity for R^4 = an aromatic moiety and zero for others. The specific effect of bromine at R^4 is, however, described by a parameter $I_{4,Br}$. Now as obvious from Eqs. 23 and 24, the positive coefficients of I_4 suggest that aromatic substituents at R^4-position will be favorable to the inhibition potency of the compounds against MMP-9 and MMP-13. However, the bromine seems to be better than any other substituent at this position for the inhibition of TACE (Eq. 25). This difference can be obviously attributed to the structural difference in the enzymes. The positive coefficients of I_3 in Eqs. 22 and 24 also suggest that aromatic substituents at that ring (ring attached to nitrogen) will favor the activity of compounds against MMP-1 as well as MMP-13. This favorable effect of aromatic substituents at R^3- and R^4-positions may be attributed to their ability to be in the plane of the ring. The positive coefficient of I_2 in Eq.(22) indicates that a substituent like CH_2-3-pyridyl will be beneficial to the inhibition of MMP-1. The beneficial role of this substituent may be obviously due to the presence in it of a nitrogen with a lone pair of electrons. This lone pair of electrons at the nitrogen may either participate in some

electronic interaction with the receptor or might affect the electronic property of the nitrogen of sulfonamide group, whose electronic character has been shown in many studies [5-7,22] to be very crucial for MMP inhibitions.

The role of bromine in TAC… case of the compounds of Table 3.19 also (E… ned for the compounds of Table 3.19 for TAC… n the case of these compounds, the bromine is fo… n also (Eq. 27).

TACE

$\log (1/IC_{50}) = 0.763(\pm0.188)I_{4,Br} - ($

$n = 19,\ r = 0.907,\ r^2_{cv} = 0.75,\ s = 0.$ (26)

MMP-1

$\log (1/IC_{50}) = 0.234(\pm0.147)I_{4,Br} +$ $- 0.534(\pm0.251)I_1$

$- 0.062(\pm0.060)$Clog

$n = 19,\ r = 0.935,\ r^2_{cv} = 0.74,\ s =$ (27)

MMP-9

$\log (1/IC_{50}) = 0.695(\pm0.172)I_3$ $)(ClogP)^2$

$+ 8.143(\pm0.122)$

$n = 19,\ r = 0.931,\ r^2_{cv} = 0.74$ 1.20 (28)

MMP-13

$\log (1/IC_{50}) = 0.410(\pm0.1$

$n = 19,\ r = 0.914,\ r^2_{cv} = 0.79,\ s = 0.19,\ F_{2,14} = 40.71(6.51)$ (29)

In MMP-1 inhibition, however, there are also some other substituents that are shown to be favorable to the activity of the compounds (Eq. 27). The positive coefficient of I_3 that has been used with a value of unity for $R^3 = CH_2N[(CH_2)_2]_2NCH_3$ [(N-

electronic interaction with the receptor or might affect the electronic property of the nitrogen of sulfonamide group, whose electronic character has been shown in many studies [5-7,22] to be very crucial for MMP inhibitions.

The role of bromine in TACE inhibition is consistently observed in the case of the compounds of Table 3.19 also (Eq. 26). Equation 26, which has been obtained for the compounds of Table 3.19 for TACE inhibition, is exactly parallel to Eq. 25. In the case of these compounds, the bromine is found to be favorable for MMP-1 inhibition also (Eq. 27).

TACE

$$\log (1/IC_{50}) = 0.763(\pm0.188)I_{4,Br} - 0.100(\pm0.063)ClogP + 6.767(\pm0.121)$$
$$n = 19,\ r = 0.907,\ r^2_{cv} = 0.75,\ s = 0.16,\ F_{2,14} = 37.28(6.51) \qquad (26)$$

MMP-1

$$\log (1/IC_{50}) = 0.234(\pm0.147)I_{4,Br} + 0.317(\pm0.186)I_3 + 0.629(\pm0.173)I_2 + 0.534(\pm0.251)I_1 - 0.062(\pm0.060)ClogP + 6.801(\pm0.150)$$
$$n = 19,\ r = 0.935,\ r^2_{cv} = 0.74,\ s = 0.13,\ F_{5,13} = 18.15(4.86) \qquad (27)$$

MMP-9

$$\log (1/IC_{50}) = 0.695(\pm0.172)I_3 - 0.154(\pm0.133)ClogP + 0.064(\pm0.039)(ClogP)^2 + 8.143(\pm0.122)$$
$$n = 19,\ r = 0.931,\ r^2_{cv} = 0.74,\ s = 0.16,\ F_{2,16} = 32.65(6.23),\ ClogP_o = 1.20 \qquad (28)$$

MMP-13

$$\log (1/IC_{50}) = 0.410(\pm0.158)Pol + 0.773(\pm0.325)I_1 + 5.960(\pm0.824)$$
$$n = 19,\ r = 0.914,\ r^2_{cv} = 0.79,\ s = 0.19,\ F_{2,14} = 40.71(6.51) \qquad (29)$$

In MMP-1 inhibition, however, there are also some other substituents that are shown to be favorable to the activity of the compounds (Eq. 27). The positive coefficient of I_3 that has been used with a value of unity for $R^3 = CH_2N[(CH_2)_2]_2NCH_3$ [(N-

methylpiperazinyl)methyl group)] suggests that such a substituent at R^3-position will have better effect than any other substituent. The reason may be that this substituent has double nitrogens and is present at the aryl ring ortho to sulfonamide nitrogen, and because of this it might change the electronic characteristics of the latter. There are, of course, some other piperazine-derived substituents at R^3-position, but only 4-methyl derivative ($CH_2N[(CH_2)_2]_2NCH_3$) is shown to be better. One can, therefore, assume that there can also be a size effect of R^3-substituent and that 4-methyl derivative gives an optimum size. Similarly, mostly nitrogen-containing R^2-substituent directly attached to sulfonamide nitrogen is shown by I_2 parameter to be more conducive than a small CH_3 group. I_2 has a value of zero for $R^2 = CH_3$ and unity for other substitutent. This effect of nitrogen-containing R^2-substituent is consistent to what we discussed about CH_2-3-pyridyl group in Table 3.18.

At R^1-position, a group like Ph-4-Cl would be preferred to a methyl group is indicated by the positive coefficient of I_1 in Eq. 27. I_1 is equal to 1 for R^1 = Ph-4-Cl and zero for $R^1 = CH_3$. This effect of Ph-4-Cl may be due to its aromatic character. If we compare this with the case of OCH_2-Ph at R^1-position in Table 3.18, we can conclude that there can also be a requirement of an optimum size of such aromatic moiety to be effective. The Ph-4-Cl is shown to be favorable to MMP-13 inhibition also (Eq. 29).

The (N-methypiperazinyl)methyl group for which I_3 parameter has been used is found to be also conductive to the MMP-9 inhibition (Eq. 28). As usual, the hydrophobicity of the molecule is shown to have the negative effect but acquires an optimum value [Clog P_o] = 1.20. Averse to hydrophobicity, a polarizability term (Pol) is found to control the activity of the compounds for the inhibition of MMP-13 (Eq. 29).

In the case of compounds of Table 3.20, the polarizability of the compounds has been shown to be a major factor in the inhibition of MMP-9 (Eq. 30). In addition to the polarizability, two structural features of R^1 moiety in compounds of Table 3.20 are found to control the activity by producing negative effect. These structural features are acetylene-derived substituents and nitrogen-containing substituents. Their effects are

described by two indicator parameters, $I_{1,CC}$ and $I_{1,N}$, respectively, with a value of 1 each for these substituents and zero for others. Both these parameters are present in Eqs. 30 and 31 with negative coefficients, suggesting that acetylene-derived or a nitrogen-containing R^1-substituent will not be favorable to MMP-9 and MMP-13 inhibitions. However, in the case of TACE inhibition (Eq. 32), $I_{1,CC}$ is found to have a positive effect

MMP-9

$$\log (1/IC_{50}) = 0.503(\pm0.477)\text{Pol} - 1.806(\pm0.567)I_{1,CC} - 0.807(\pm0.559)I_{1,N} + 5.916(\pm2.137)$$

$$n = 16,\ r = 0.920,\ r^2_{cv} = 0.64,\ s = 0.37,\ F_{3,12} = 21.92(5.95) \qquad (30)$$

MMP-13

$$\log (1/IC_{50}) = 8.220(\pm0.467) - 0.320(\pm0.192)\text{ClogP} - 0.891(\pm0.422)I_{1,CC} - 0.531(\pm0.403)I_{1,N}$$

$$n = 17,\ r = 0.910,\ r^2_{cv} = 0.70,\ s = 0.29,\ F_{3,13} = 20.78(5.74) \qquad (31)$$

TACE

$$\log (1/IC_{50}) = 0.491(\pm0.258)I_{1,CC} + 0.429(\pm0.280)I_{4,Br} - 0.891(\pm0.309)I_{1,N} - 0.284(\pm0.122)\text{ClogP} + 7.457(\pm0.342)$$

$$n = 18,\ r = 0.905,\ r^2_{cv} = 0.64,\ s = 0.19,\ F_{4,13} = 14.79(5.20) \qquad (32)$$

MMP-1

$$\log (1/IC_{50}) = 7.276(\pm0.549) - 0.596(\pm0.234)\text{ClogP}$$

$$n = 9,\ r = 0.916,\ r^2_{cv} = 0.67,\ s = 0.22,\ F_{1,7} = 36.46(12.25) \qquad (33)$$

but $I_{1,N}$ a negative effect. Acetylene-derived substituents are long linear chains and thus might be creating steric-problems while interacting, presumably, with the active sites of MMP-9 and MMP-13, but in TACE the active site may be capable of accommodating them well. Nitrogen-containing substituents, that are unfavorable to TACE also, might be eliciting their negative effect through some unwanted electronic interactions with the enzyme. For the TACE inhibition, bromine at R^4, as usual, is shown to be better than any

other R^4-substituent (Eq. 32) The MMP-1 inhibition is not found to be affected by any other parameter except ClogP, which is showing a negative effect (Eq. 33).

From this QSAR study we find that in anthranilic hydroxamic acid-based MMP inhibitors the hydrophobic character of the molecules is not beneficial to the activity and in almost all the cases it has the adverse effect. Thus it appears that matrix metalloproteinases provide little opportunity to the molecules to have hydrophobic interactions, instead there can be strong electronic interactions between them, in which the sulfonamide group present in the molecules might play a major role in addition to the hydroxamic acid moiety chelating with the zinc atom of the MMPs. QSAR study points out that the interaction of sulfonamide group with the enzyme can be greatly helped by the presence of the substituents of high electronic characteristics at the sulfonamide nitrogen or at the aromatic rings, affecting the electronic properties of nitrogen or sulfur or of both of sulfonamide group. The large substituents at the aromatic rings however might sometimes produce some steric problems, but those having some electronic character and being of reasonable size might have some electronic interactions with the receptors.

3.4 Bicyclic Heteroaryl Hydroxamic Acid Analogs

The series of bicyclic heteroaryl hydroxamic acid analogs (**5** and **6**) reported by Zask et al [23] are listed in Tables 3.25 and 3.26 with their physicochemical parameters that were found to be correlated with the MMP/TACE inhibition potencies of the compounds. The inhibition potencies of compounds, observed as well as calculated from correlations obtained, are listed in Tables 3.27 and 3.28, respectively. The most important physicochemical properties that were found to be correlated with the activities of the compounds were calculated hydrophobicity parameter (ClogP), polarizability (Pol), and molar volume (MV).

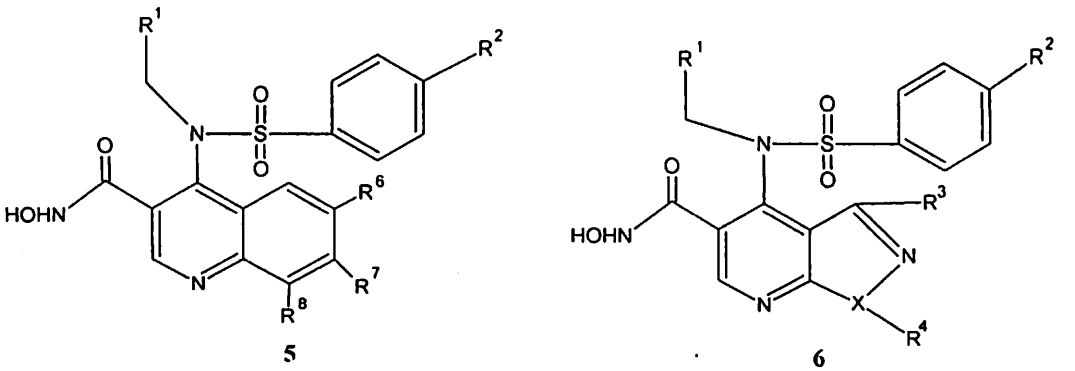
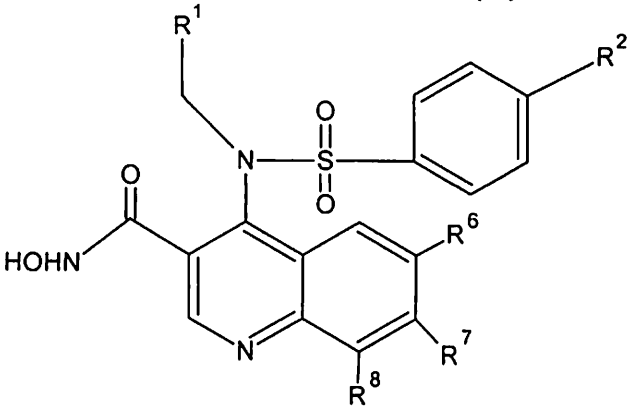


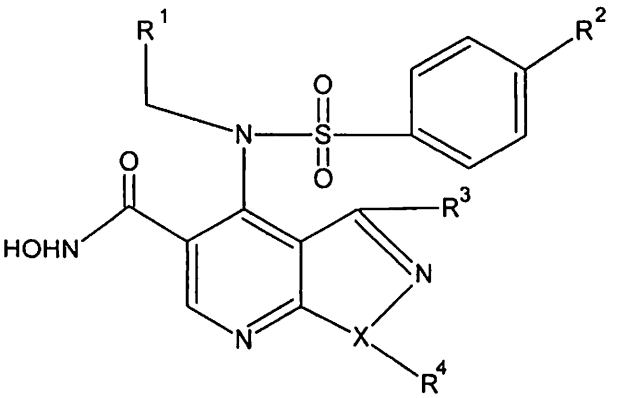
Figure 3.4. A series of bicyclic heteroaryl hydroxamic acid analogs

Table 3.25. A series of quinoline analogues (**5**) and related physicochemical parameter(s).



Compd	R^1	R^2	R^6	R^7	R^8	ClogP	$I_{2,M}$	$I_{6,X}$	$I_{7,X}$
1	C_6H_5	OCH_3	Br	H	H	3.590	1	1	0
2	C_6H_5	OCH_3	H	Br	H	3.590	1	0	1
3	H	OCH_3	H	H	Br	1.820	1	0	0
4	3-pyridyl	OCH_3	H	H	Br	2.090	1	0	0
5	C_6H_5	OCH_3	CF_3	H	H	3.610	1	1	0
6	3-pyridyl	OCH_3	H	CF_3	H	2.120	1	0	1
7	C_6H_5	OCH_3	H	CF_3	H	3.610	1	0	1
8	C_6H_5	OCH_3	H	H	CF_3	3.610	1	0	0
9	3-pyridyl	OCH_3	H	H	I	2.350	1	0	0
10	3-pyridyl	OCH_3	H	H	OCH_3	1.460	1	0	0
11	3-pyridyl	OCH_3	H	H	C_6H_5	3.060	1	0	0
12	3-pyridyl	OCH_3	H	H	2-thienyl	2.910	1	0	0
13	3-pyridyl	OCH_3	H	H	$CH_2C_6H_5$	3.240	1	0	0
14	H	OCH_3	H	H	vinyl	1.620	1	0	0
15	C_6H_5	OCH_3	H	H	CH_3	3.310	1	0	0
16	C_6H_5	OCH_3	H	H	CH_2CH_3	3.840	1	0	0
17	C_6H_5	OCH_3	H	H	iPr	4.240	1	0	0
18	C_6H_5	OCH_3	H	H	tBu	4.630	1	0	0
19	3-pyridyl	C_6H_5	H	CF_3	H	4.140	0	0	1
20	3-pyridyl	CH_3	H	CF_3	H	2.750	0	0	1
21	H	O-4-pyridyl	H	H	H	3.200	0	0	0
22	H	OCH_2CCCH_3	H	H	Br	4.760	0	0	0
23	H	OCH_2CCCH_3	H	H	OCH_3	4.120	0	0	0

Table 3.26. A series of heterobicyclic analogs (**6**) and related physicochemical parameter(s).



Compd	R^1	R^2	R^3	R^4	X	ClogP	Pol	MV	$I_{2,CC}$	$I_{1,A}$
1	3-pyridyl	OCH_3	CH_3	CH_3	N	-0.086	5.000	3.310	0	1
2	3-pyridyl	OCH_3	H	C_6H_5	N	1.584	5.650	3.690	0	1
3	3-pyridyl	OCH_3	CH_3	C_6H_5	N	1.853	5.820	3.840	0	1
4	3-pyridyl	OCH_3	CH_3	-	O	0.293	4.670	3.160	0	1
5	3-pyridyl	OCH_3	CH_3	-	S	0.765	4.900	3.230	0	1
6	H	F	CH_3	CH_3	N	-0.383	3.820	2.550	0	0
7	H	OC_4H_9	CH_3	CH_3	N	1.230	4.610	3.220	0	0
8	H	OC_6H_4-4-Cl	CH_3	CH_3	N	2.285	5.060	3.360	0	0
9	H	O-4-pyridyl	CH_3	CH_3	N	0.075	4.820	3.150	0	0
10	H	OCH_2CCCH_3	CH_3	CH_3	N	0.772	4.610	3.220	1	0
11	H	OCH_2CCCH_3	CH_3	-	O	1.151	4.350	2.950	1	0
12	H	OCH_2CCCH_3	CH_3	-	S	1.623	4.480	3.020	1	0

Table 3.27. Observed and calculated MMP and TACE inhibition potencies of compounds of Table 3.25. Observed activities have been taken from ref. [23].

	log (1/IC_{50})											
	MMP-1			MMP-9			MMP-13			TACE		
Compd	Obsd	Calcd Eq. 34	Loo	Obsd	Calcd Eq. 35	Loo	Obsd	Calcd Eq. 36	Loo	Obsd	Calcd Eq. 37	Loo
1	6.97	6.79	6.76	8.10	8.03	7.96	8.22	8.27	8.27	-	5.91	-
2	6.76	6.79	6.79	7.96	7.87	7.84	8.15	8.27	8.28	-	6.72	-
3	6.65	7.10	7.20	8.70	8.78	8.80	8.70	8.97	9.03	6.53	6.72	6.77
4	7.19	7.05	7.03	8.70	8.73	8.74	9.00	8.86	8.84	6.91	6.78	6.75
5	6.76	6.78	6.78	7.96	8.03	8.10	8.15	8.26	8.27	-	6.65	-
6	7.11	7.04	7.03	8.40	8.11	7.94	9.00	8.85	8.83	6.00	6.03	6.09
7	6.76	6.78	6.78	7.96	7.87	7.83	8.15	8.26	8.27	-	5.90	-
8	6.03[a]	6.78	-	8.70	8.49	8.46	9.00[c]	8.26	-	6.72	6.65	6.64
9	7.12	7.00	6.99	8.52	8.69	8.72	8.52	8.76	8.79	6.91	6.81	6.79
10	7.34	7.16	7.09	8.70	8.84	8.89	9.00	9.11	9.15	6.65	6.61	6.60
11	6.82	6.88	6.88	8.52	8.58	8.58	8.40	8.48	8.48	6.92	6.78	6.75
12	6.87	6.90	6.91	8.70	8.60	8.59	8.70	8.54	8.53	6.79	6.80	6.79
13	7.00	6.85	6.83	8.40	8.55	8.57	8.52	8.41	8.40	6.47	6.75	6.81
14	6.70[a]	7.13	-	8.30[b]	8.81	-	8.30[c]	9.05	-	6.69	6.67	6.66
15	6.82	6.83	6.83	-	8.54	-	7.59[c]	8.38	-	6.20[d]	6.73	-
16	6.72	6.74	6.74	8.70	8.45	8.41	8.40	8.17	8.15	6.50	6.57	6.58
17	6.46	6.67	6.73	8.22	8.39	8.43	8.05	8.01	8.01	6.23	6.39	6.44
18	5.51[a]	6.60	-	8.10	8.32	8.43	7.80	7.86	7.87	6.40	6.16	5.85
19	5.38	5.85	6.00	5.93	6.40	7.06	7.30[c]	8.05	-	6.91	6.87	6.82
20	-	6.09	-	-	6.63	-	-	8.60	-	-	7.25	-
21	5.99	6.01	6.02	9.00[b]	7.16	-	9.00	8.42	8.39	6.91[d]	7.94	-
22	6.02	5.74	5.62	-	6.91	-	7.57	7.81	7.87	7.09	7.26	7.44
23	6.06	5.85	5.78	7.48	7.02	6.35	8.05	8.06	8.06	7.77	7.63	7.51

[a]Not included in the derivation of Eq. 34.
[b]Not included in the derivation of Eq. 35.
[c]Not included in the derivation of Eq. 36.
[d]Not included in the derivation of Eq. 37.

Table 3.28. Observed and calculated MMP and TACE inhibition potencies of compounds of Table 3.26. Observed activities have been taken from ref. [23].

	log (1/IC_{50})											
	MMP-1			MMP-9			MMP-13			TACE		
Compd	Obsd	Calcd Eq. 38	Loo	Obsd	Calcd Eq. 39	Loo	Obsd	Calcd Eq. 40	Loo	Obsd	Calcd Eq. 41	Loo
1	7.41	7.55	7.92	8.70	8.88	8.93	8.70	8.88	8.93	6.80	6.73	6.71
2	6.04	6.33	6.52	8.22[b]	8.94	-	7.70[c]	8.26	-	6.36	5.26[d]	-
3	6.94	6.62	6.38	8.70[b]	9.08	-	8.52[c]	8.25	-	6.86	4.67[d]	-
4	6.95	6.82	6.76	8.05	8.16	8.18	8.00	8.31	8.37	6.83	7.32	7.40
5	6.26	6.28	6.29	8.70	8.66	8.66	8.52	8.71	8.75	6.27	7.04[d]	-
6	6.75[a]	7.84	-	6.23	6.30	6.66	6.77	6.84	7.24	-	9.68	-
7	5.72	5.70	5.69	8.15	8.03	8.00	8.52	8.21	8.15	7.07	7.08	7.09
8	6.94	6.90	6.76	9.00	9.01	9.02	9.00	8.99	8.98	6.45	6.54	6.60
9	5.74[a]	6.74	-	8.70	8.49	8.45	9.00	8.57	8.49	-	7.35	-
10	6.00	5.81	5.73	7.00	7.16	7.25	7.00	7.10	7.15	7.52	7.08	7.00
11	5.72	5.69	5.68	6.61	6.59	6.58	6.61	6.65	6.67	8.22	8.13	8.03
12	5.63	5.90	5.98	7.02	6.88	6.81	7.02	6.88	6.81	7.85	7.86	7.86

[a]Not included in the derivation of Eq. 38.
[b]Not included in the derivation of Eq. 39.
[c]Not included in the derivation of Eq. 40.
[d]Not included in the derivation of Eq. 41.

For the series of 5 (Table 3.25), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 0.840(\pm0.292)I_{2,M} - 0.176(\pm0.136)ClogP + 6.576(\pm0.597)$$
$$n = 19,\ r = 0.914,\ r^2_{cv} = 0.73,\ s = 0.21,\ F_{2,16} = 40.75(6.23) \quad (34)$$

MMP-9

$$\log (1/IC_{50}) = 1.391(\pm0.440)I_{2,M} - 0.461(\pm0.414)I_{6,X} - 0.619(\pm0.312)I_{7,X} - 0.161(\pm0.153)ClogP + 7.680(\pm0.747)$$
$$n = 18,\ r = 0.945,\ r^2_{cv} = 0.60,\ s = 0.25,\ F_{4,13} = 27.28(5.20) \quad (35)$$

MMP-13

$$\log (1/IC_{50}) = 9.691(\pm0.382) - 0.396(\pm0.114)ClogP$$
$$n = 18,\ r = 0.879,\ r^2_{cv} = 0.73,\ s = 0.21,\ F_{1,16} = 54.63(8.53) \quad (36)$$

TACE

$$\log (1/IC_{50}) = 0.800(\pm0.657)ClogP - 0.155(\pm0.109)(ClogP)^2 - 1.184(+0.321)I_{2,M} - 0.746(\pm0.303)I_{7,X} + 6.965(+0.303)$$
$$n = 16,\ r = 0.934,\ r^2_{cv} = 0.67,\ s = 0.17,\ F_{4,11} = 18.87(5.67),\ ClogP_o = 2.58 \quad (37)$$

Now as obvious, Eqs. (34)-(36) suggest that for all the 3 MMPs (MMP-1, MMP-9, and MMP-13) treated here, the hydrophobic property of the compounds is not conducive to their inhibition potencies. However, the occurrence of $I_{2,M}$ parameter with a positive coefficient in Eqs. (34) and (35) indicates that the presence of a methoxy group at R^2-position will be advantageous to the inhibition of MMP-1 and MMP-9, but the presence of $I_{6,X}$ and $I_{7,X}$ variables with negative coefficients in Eq. (35) suggests that this positive effect of methoxy group in MMP-9 inhibition can be offset by the presence of a halogen or halogen-containing group at R^6- or R^7-position. In the case of MMP-13 inhibition, however, none of these indicator variables could crop up (Eq. 36) and thus the sole effect is of the hydrophobicity of the molecules.

For the TACE inhibition, the hydrophobicity is shown to initially increase the activity (Eq. 37), but since the correlation is parabolic in logP, the activity is optimized with an optimum value of ClogP = 2.58, beyond which the activity will start decreasing as the value of ClogP will increase. Additionally, not only a halogen or halogen-containing group at R^7-postion will not be conductive to the inhibition of this enzyme, but even a methyl group at R^2-position will not be advantageous to it.

The negative roles in MMP-9 and TACE inhibitions of halogen or halogen-containing groups at R^6- or R^7-position lead to suggest that in these two enzymes there can be a repulsive interaction between the lone-pair electrons present in these groups and some negatively charged sites in the enzyme. Most of the sites in MMPs seem to be of electronic nature and that is why probably the hydrophobicity of molecules in most of the cases does not favor the inhibition of these enzymes.

For the series of **6** (Table 3.26), the correlations obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 6.895(\pm 0.588) - 2.116(\pm 0.882)ClogP + 0.928(\pm 0.372)(ClogP)^2 + 0.462(\pm 0.408)I_{1,A}$$

$$n = 10,\ r = 0.954,\ r^2_{cv} = 0.71,\ s = 0.24,\ F_{3,6} = 20.12(9.78),\ ClogP_o = 1.14 \qquad (38)$$

MMP-9

$$\log (1/IC_{50}) = 2.192(\pm 0.340)Pol - 0.866(\pm 0.256)I_{2,CC} - 2.077(\pm 1.603)$$

$$n = 10,\ r = 0.991,\ r^2_{cv} = 0.95,\ s = 0.15,\ F_{2,7} = 199.82(9.55) \qquad (39)$$

MMP-13

$$\log (1/IC_{50}) = 1.730(\pm 0.596)Pol - 1.106(\pm 0.449)I_{2,CC} + 0.233(\pm 2.810)$$

$$n = 10,\ r = 0.971,\ r^2_{cv} = 0.88,\ s = 0.26,\ F_{2,7} = 56.77(9.55) \qquad (40)$$

TACE

$\log (1/IC_{50}) = 19.576(\pm 6.749) - 3.880(\pm 2.122)MV$

$n = 7, r = 0.903, r^2_{cv} = 0.73, s = 0.30, F_{1,5} = 22.09(16.26)$ (41)

In this case, the electronic nature of the active sites in the MMPs, particularly in MMP-9 and MMP-13, has surfaced more vividly. For these two MMPs, the polarizability of the molecules appears to play the dominant role (Eqs. 39 and 40) and this polarizability effect of this group of molecules is very well afforded by the presence of more number of heteroatoms in their bicyclic ring.

MMP-9 and MMP-13 appear to behave in a similar manner with the derivatives of **6**, as Eqs. (39) and (40) obtained for them are parallel. In these two equations, there is an indicator variable $I_{2,CC}$ that has been used for a butynyloxy group at R^2-position. This variable has a value of unity for this group and zero for any other group. Its negative coefficient in both Eqs. (39) and (40), therefore, suggests that such a group will have a detrimental effect for both MMP-9 and MMP-13 inhibitions. This negative effect of butynyloxy group at R^2-position may be attributed to its bulky size as compared to that of a methoxy group.

For TACE inhibition, the molecular volume is shown to control the activity (Eq. 41). Highly voluminous molecules will not be tolerated. Hydrophobicity of the molecules is found to be effective only in the case of MMP-1 inhibition (Eq. 38). Equation 38 shows that hydrophobicity would initially decrease the activity but after a certain optimum value of ClogP ($ClogP_o$ = 1.14), the activity would start increasing with the increase in the ClogP value. In Eq. (38), there is an indicator variable $I_{1,A}$ that describes the effect of a 3-pyridyl group at R^1-position. $I_{1,A}$ has a value of 1 for this group and zero for others. A positive coefficient of this variable indicates an advantageous effect of 3-pyridyl group at R^1-position to the inhibition potency of the compounds against MMP-1. Again, the reason to this advantageous effect of 3-pyridyl group may attributed to its electronic nature because of a nitrogen in it. A pyridyl group may well be involved in some electronic interaction with the receptor.

3.5 Pyranyl Hydroxamic Acid Analogs

Recently two different series of hydroxamic acids (7 and 8) that contain mostly a pyran-type of ring in the back bone attached directly to the carbonyl carbon of the hydroxamic acid moiety are reported for the specific inhibition against MMPs. These two series differ in that in one (7) the pyran-type ring is attached on the other side to a phenylsulfonyl amino group and in the other one (8) the same is attached to a simple phenylsulfonyl group. The series 7 has been reported by Reiter et al. [24] and series 8 by Noe et al. [25]. Both the series of compounds (7 and 8) are listed in Tables 3.29 and 3.30, respectively, along with their physicochemical parameters that were found to be correlated with their MMP inhibition potencies. The inhibition potencies of compounds, observed as well as calculated from correlations obtained, are listed in Tables 3.31 and 3.32, respectively. In these Tables, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. The physicochemical parameters found to be useful in this QSAR study are the hydrophobic constant π and the electronic constant σ (Hammett constant) of the substituents. Some indicator variables were also used to account for the effects of some specific structural features in the compounds. These variables have been defined in the text as and when they have appeared.

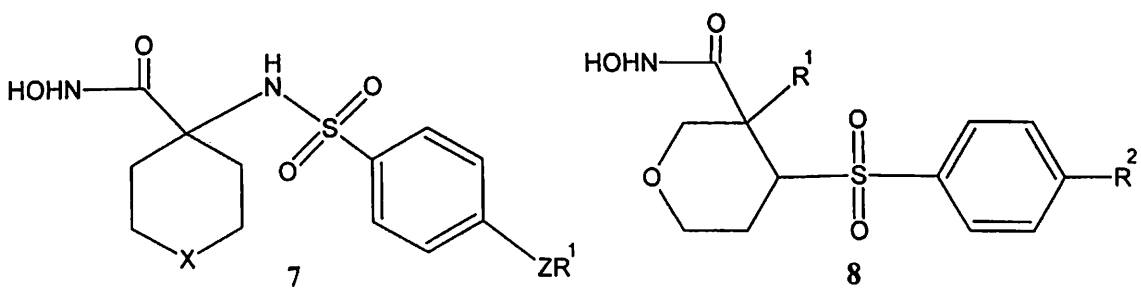
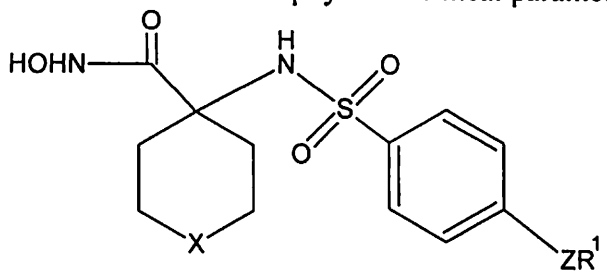


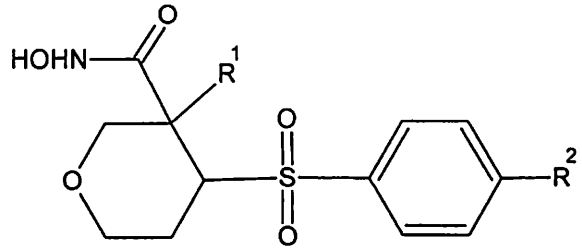
Figure 3.5. A series of pyranyl hydroxamic acid analogs

Table 3.29. Analogs of series **7** and related physicochemical parameter(s).



Compd	X	Z	R^1	$\pi_2(R^1)$	$\pi_{3,4}(R^1)$	I_{1A}
1	O	O	C_6H_5	0.000	0.000	1
2	O	O	C_6H_4-2-F	0.140	0.000	1
3	O	O	C_6H_4-3-F	0.000	0.140	1
4	O	O	C_6H_4-4-F	0.000	0.140	1
5	O	O	C_6H_4-2-Cl	0.710	0.000	1
6	O	O	C_6H_4-3-Cl	0.000	0.140	1
7	O	O	C_6H_4-4-Cl	0.000	0.710	1
8	O	O	C_6H_4-4-OCH_3	0.000	-0.020	1
9	O	O	C_6H_4-4-NC	0.000	-0.570	1
10	O	O	1-naphthyl	0.000	0.000	0
11	O	O	2-naphthyl	0.000	0.000	0
12	O	O	$CH_2C_6H_5$	0.000	0.000	0
13	O	O	$CH_2C_6H_4$-2-F	0.140	0.000	0
14	O	O	$CH_2C_6H_4$-3-F	0.000	0.140	0
15	O	O	$CH_2C_6H_4$-4-F	0.000	0.140	0
16	O	O	2-pyridyl	0.000	0.000	0
17	O	O	3-pyridyl	0.000	0.000	0
18	O	O	4-pyridyl	0.000	0.000	0
19	O	O	2-pyridyl-5-F	0.000	0.140	0
20	O	O	2-pyridyl-5-Cl	0.000	0.710	0
21	O	S	C_6H_4-4-F	0.000	0.140	1
22	O	-	C_6H_4-4-F	0.000	0.140	1
23	S	O	C_6H_4-4-F	0.000	0.140	1
24	SO_2	O	C_6H_4-4-F	0.000	0.140	1

Table 3.30. Analogs of series **8** and related physicochemical parameter(s).



Compd	R^1	R^2	$\pi_2(R^2)$	$\pi_4(R^2)$	$\sigma_2(R^2)$	I_1	I_{2A}
1	OH	$OCH_2C_6H_4$-2-CH_3	0.560	0.000	-0.170	0	0
2	OH	$OCH_2C_6H_4$-3-CH_3	0.000	0.000	0.000	0	0
3	OH	$OCH_2C_6H_4$-4-CH_3	0.000	0.560	0.000	0	0
4	OH	$OCH_2C_6H_4$-2-Cl	0.710	0.000	0.230	0	0
5	OH	$OCH_2C_6H_4$-3-Cl	0.000	0.000	0.000	0	0
6	OH	$OCH_2C_6H_4$-4-Cl	0.000	0.710	0.000	0	0
7	OH	$OCH_2C_6H_4$-2-CF_3	0.100	0.000	0.540	0	0
8	OH	$OCH_2C_6H_3$-2,3-$(Cl)_2$	0.710	0.000	0.230	0	0
9	OH	$OCH_2C_6H_3$-2,4-$(Cl)_2$	0.710	0.710	0.230	0	0
10	OH	$OCH_2C_6H_3$-2,5-$(Cl)_2$	0.710	0.000	0.230	0	0
11	OH	$OCH_2C_6H_3$-2,6-$(Cl)_2$	0.710	0.000	0.000	0	0
12	OH	$OCH_2C_6H_3$-2,4-$(CH_3)_2$	0.560	0.560	-0.170	0	0
13	OH	$OCH_2C_6H_3$-2,5-$(CH_3)_2$	0.560	0.000	-0.170	0	0
14	OH	$OCH_2C_6H_3$-2,6-$(CH_3)_2$	0.560	0.000	0.000	0	0
15	OH	OC_6H_4-2-CH_3	0.560	0.000	0.000	0	1
16	OH	OC_6H_4-3-CH_3	0.000	0.000	0.000	0	1
17	OH	OC_6H_4-4-CH_3	0.000	0.560	0.000	0	1
18	OH	C_6H_4-2-CH_3	0.560	0.000	0.000	0	0
19	OH	C_6H_4-3-CH_3	0.000	0.000	0.000	0	0
20	OH	C_6H_4-4-CH_3	0.000	0.560	0.000	0	0
21	OCH_3	$OCH_2C_6H_4$-2-Cl	0.710	0.000	0.230	1	0
22	OCH_3	$OCH_2C_6H_3$-2,4-$(Cl)_2$	0.710	0.710	0.230	1	0

Table 3.31. Observed and calculated MMP inhibition potencies of compounds of Table 3.29. Observed activities have been taken from ref. [24].

	log ($1/IC_{50}$)					
	MMP-1			MMP-13		
Compd	Obsd	Calcd Eq. 42	Loo	Obsd	Calcd Eq. 43	Loo
1	6.31	6.06	6.06	8.82	8.91	8.92
2	6.74[a]	6.06	-	9.19	8.75	8.70
3	5.96	6.20	6.23	9.25	8.91	8.87
4	6.38	6.20	6.18	9.12	8.91	8.89
5	5.77	6.06	6.10	8.01	8.09	9.12
6	5.41[a]	6.20	-	8.34[b]	8.91	-
7	6.49	6.75	6.92	8.92	8.91	8.91
8	6.11	6.04	6.04	9.06	8.91	8.89
9	5.32	5.51	5.66	8.77	8.91	8.93
10	5.31	5.13	5.11	6.68[b]	7.95	-
11	5.41	5.13	5.09	8.30	7.95	7.90
12	5.27	5.13	5.11	8.19	7.95	7.92
13	5.02	5.13	5.14	7.72	7.79	7.96
14	5.06	5.26	5.29	7.62	7.95	7.99
15	5.19	5.26	5.27	7.96	7.95	7.95
16	4.92	5.13	5.15	7.89	7.95	7.96
17	6.26[a]	5.13	-	7.60	7.95	7.99
18	4.92	5.13	5.15	8.24	7.95	7.91
19	5.42	5.26	5.25	7.85	7.95	7.96
20	5.85	5.81	5.79	8.82[b]	7.95	-
21	5.23[a]	6.20	-	8.34[b]	8.91	-
22	6.70	6.20	6.14	8.36	8.91	8.97
23	6.12	6.20	6.21	8.82	8.91	8.92
24	6.26	6.20	6.19	8.70	8.91	8.93

[a]Not included in the derivation of Eq. 42.
[b]Not included in the derivation of Eq. 43.

Table 3.31. Observed and calculated MMP inhibition potencies of compounds of Table 3.29. Observed activities have been taken from ref. [24].

	log (1/IC_{50})					
	MMP-1			MMP-13		
Compd	Obsd	Calcd Eq. 42	Loo	Obsd	Calcd Eq. 43	Loo
1	6.31	6.06	6.06	8.82	8.91	8.92
2	6.74[a]	6.06	-	9.19	8.75	8.70
3	5.96	6.20	6.23	9.25	8.91	8.87
4	6.38	6.20	6.18	9.12	8.91	8.89
5	5.77	6.06	6.10	8.01	8.09	9.12
6	5.41[a]	6.20	-	8.34[b]	8.91	-
7	6.49	6.75	6.92	8.92	8.91	8.91
8	6.11	6.04	6.04	9.06	8.91	8.89
9	5.32	5.51	5.66	8.77	8.91	8.93
10	5.31	5.13	5.11	6.68[b]	7.95	-
11	5.41	5.13	5.09	8.30	7.95	7.90
12	5.27	5.13	5.11	8.19	7.95	7.92
13	5.02	5.13	5.14	7.72	7.79	7.96
14	5.06	5.26	5.29	7.62	7.95	7.99
15	5.19	5.26	5.27	7.96	7.95	7.95
16	4.92	5.13	5.15	7.89	7.95	7.96
17	6.26[a]	5.13	-	7.60	7.95	7.99
18	4.92	5.13	5.15	8.24	7.95	7.91
19	5.42	5.26	5.25	7.85	7.95	7.96
20	5.85	5.81	5.79	8.82[b]	7.95	-
21	5.23[a]	6.20	-	8.34[b]	8.91	-
22	6.70	6.20	6.14	8.36	8.91	8.97
23	6.12	6.20	6.21	8.82	8.91	8.92
24	6.26	6.20	6.19	8.70	8.91	8.93

[a]Not included in the derivation of Eq. 42.
[b]Not included in the derivation of Eq. 43.

Table 3.32. Observed and calculated MMP inhibition potencies of compounds of Table 3.30. Observed activities have been taken from ref. [25].

	log ($1/IC_{50}$)								
	MMP-1			MMP-13			Aggrecanase		
Compd	Obsd	Calcd Eq. 44	Loo	Obsd	Calcd Eq. 45	Loo	Obsd	Calcd Eq. 46	Loo
1	4.92	4.84	4.83	7.68[b]	6.88	-	7.26	7.42	7.54
2	4.66	4.84	4.88	8.30	8.71	8.80	-	7.23	-
3	5.27	5.03	4.87	8.89	9.15	9.20	-	7.23	-
4	5.55[a]	4.84	-	8.57	8.19	8.06	7.40[c]	6.98	-
5	5.10	4.84	4.80	8.62	8.71	8.74	-	7.23	-
6	5.85	5.95	6.04	9.06	9.26	9.33	6.48[c]	7.23	-
7	-	4.84	-	7.55	7.61	7.63	6.66	6.65	6.63
8	4.89	4.84	4.84	7.82	8.19	8.33	6.85	6.98	7.01
9	6.04	5.95	5.85	9.02	8.74	8.56	8.09[c]	6.98	-
10	4.57	4.84	4.89	7.89	8.19	8.31	7.06	6.98	6.97
11	-	4.84	-	-	8.20	-	-	6.98	-
12	4.72	5.03	5.25	7.77	7.32	7.02	6.43[c]	7.42	-
13	-	4.84	-	6.52	6.89	7.04	7.59	7.42	7.29
14	-	4.84	-	-	6.88	-	-	7.42	-
15	5.33[a]	6.65	-	8.01[b]	6.88	-	-	7.42	-
16	6.57	6.65	6.78	8.96	8.71	8.67	-	7.23	-
17	6.92	6.84	6.70	9.00	9.15	9.18	-	7.23	-
18	5.00	4.84	4.81	6.85	6.89	6.90	-	7.42	-
19	-	4.84	-	9.37	8.71	8.58	-	7.23	-
20	-	4.84	-	9.41	9.15	9.10	-	7.23	-
21	-	4.81	-	7.42	7.10	6.68	7.00	6.98	6.98
22	-	5.95	-	7.34	7.65	8.09	7.00	6.98	6.98

[a]Not included in the derivation of Eq. 44.
[b]Not included in the derivation of Eq. 45.
[c]Not included in the derivation of Eq. 46.

For the compounds of series 7 (Table 3.29), the correlations obtained were:

MMP-1

$$\log (1/IC_{50}) = 0.935(\pm 0.219)I_{1A} + 0.961(\pm 0.429)\pi_{3,4}(R^1) + 5.128(\pm 0.162)$$
$$n = 20,\ r = 0.924,\ r^2_{cv} = 0.79,\ s = 0.23,\ F_{2,17} = 49.42(6.11) \qquad (42)$$

MMP-13

$$\log (1/IC_{50}) = 0.962(\pm 0.265)I_{1A} - 1.163(\pm 0.840)\pi_2(R^1) + 7.948(\pm 0.193)$$
$$n = 20,\ r = 0.884,\ r^2_{cv} = 0.69,\ s = 0.27,\ F_{2,17} = 30.30(6.11) \qquad (43)$$

In Eq. (42), $\pi_{3,4}(R^1)$ refers to the hydrophobic constant of 3- or 4- position substituent in R^1-moiety in ZR^1 group. Similarly in equation (43), $\pi_2(R^1)$ refers to the hydrophobic constant of a 2-position substituent in R^1. In both equations (42) and (43), I_{1A} is an indicator variable used for an R^1-moiety which is phenyl or substituted phenyl group. For such a group I_{1A} is equal to 1 and for others it is zero. Now a positive coefficient of this variable in both the equations suggests that for both MMP-1 as well as MMP-13 inhibitions a phenyl or substituted phenyl R^1-moiety would be preferred to any other kind of R^1-moiety. Further, for MMP-1 inhibition, equation (42) indicates that if substituted phenyl group has a hydrophobic susbtituent at 3- or 4- position, the group will have an enhanced effect. Since $\pi_{3,4}$ has been defined for 3- or 4- position substituent at any kind of ring, the hydrophobic nature of such substituents at any ring, e.g. even at benzyl ring (compds 14 and 15, Table 3.29), will have a positive effect on the activity of the compounds. It can therefore be assumed that 3- or 4- position substituents might be involved in some hydrophobic interaction with the enzymes and this interaction may have an optimium effect with a phenyl group. In this case (MMP-1), however, 2-position substituents were not found to produce any effect. On the other hand, in the case of MMP-13 inhibition, the hydrophobic 2-position substituents are shown to be deterimental to the activity of the compounds (Equation (43)) and the 3,4- position substituents are found to have no effect.

In Table 3.29, a slight variation is shown in the heteroatom X in the pyran ring and in the Z moiety attached to the aryl ring. Our QSAR analysis did not show any effect of this variation.

For the series of **8** (Table 3.30), the correlations obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 4.843(\pm0.202) - 4.207(\pm3.357)\pi_4(R^2) + 8.113(\pm5.153)[\pi_4(R^2)]^2 + 1.806(\pm0.413)I_{2A}$$

$$n = 12,\ r = 0.971,\ r^2_{cv} = 0.87,\ s = 0.22,\ F_{3,8} = 43.21(7.59),\ \pi_4(R^2)_{opt} = 0.26 \qquad (44)$$

MMP-13

$$\log (1/IC_{50}) = 0.772(\pm0.625)\pi_4(R^2) - 12.768(\pm4.248)\pi_2(R^2) + 16.953(\pm6.207)[\pi_2(R^2)]^2 - 1.088(\pm0.692)I_1 + 8.715(\pm0.326)$$

$$n = 18,\ r = 0.926,\ r^2_{cv} = 0.68,\ s = 0.38,\ F_{4,13} = 19.60(5.20),\ \pi_2(R^2)_{opt} = 0.38 \qquad (45)$$

Aggrecanase

$$\log (1/IC_{50}) = 7.234(\pm0.148) - 1.090(\pm0.523)\sigma_2(R^2)$$

$$n = 7,\ r = 0.923,\ r^2_{cv} = 0.63,\ s = 0.13,\ F_{1,5} = 28.71(16.26) \qquad (46)$$

In this series, the variations are shown not only in the substituents at the aryl ring (R^2) but also in the substituents at the pyran ring (R^1). In the above equations, $\pi_x(R^2)$ or $\sigma_x(R^2)$ means the hydrophobic or electronic constant for the substituent at the x-position in the aryl ring of R^2-substituent. Thus Eq. (44) suggests that for MMP-1 inhibition, the inhibition potency of the compounds will initially decrease with the increase in hydrophobic property of 4-position substituent and then after the optimum value of $\pi_4(R^2)$ = 0.26, the potency will start increasing. However, for MMP-13, Eq. (45) indicates that such an effect would be produced by 2-position substituent and the 4-position substituent will have a linearly increasing effect.

In Eq. (44), however, there is an indicator parameter I_{2A} which has been used with a value of 1 for an R^2-substituent which is phenoxy group or substituted phenoxy group. This is almost equivalent to I_{1A} in Eq. (42) if we consider the whole ZR^1 group in **7**. Thus, like I_{1A} in Eq. (42), the positive coefficient of I_{2A} in equation (44) also suggests that for MMP-1 inhibition substituted or unsubstituted phenoxy group at the aryl ring would be advantageous to the potency of this series of compounds as compared to any other group. Other group is mostly benzyloxy group, which is slightly flexible as compared to the phenoxy group and this flexibility of benzyloxy group might be responsible for its inferior effect.

In Eq. (45), I_{2A} however has not surfaced, denying any supermacy of phenoxy substituents for MMP-13 inhibition. On the other hand, another indicator variable, I_1, has appeared, which stands for $R^1 = OCH_3$. Its value is 1 for $R^1 = OCH_3$ and zero for $R^1 =$ OH. A negative coefficient of it suggests that as compared to OH group, a methoxy group at R^1 will not be advantageous. This might be due to a steric effect.

For aggrecanase, only the electronic character of 2-position substituent in the aryl ring in R^2 is shown to control the activity (Eq. (46)).

As discussed above, we find that there are some variations in the effect of substituents at the aryl moiety in R^2-group in **8** and in equivalent ZR^1-group in **7**. The reason of this may be that the pyran ring in **7** is attached to the phenyl group through a sulfonyl amino bridge group, while in **8** it is attached through only a sulfonyl bridge group.

3.6 Piperidine Sulfonamide Aryl Hydroxamic Acid Analogs

Barta et al. [26,27] synthesized a series of piperidine sulfonamide aryl hydroxamic acid analogs (**10** and **11**). These two series were not structurally different from each other and could be represented by a general structure as **9**. This allowed us to make a detailed study on the effect of structural variation.

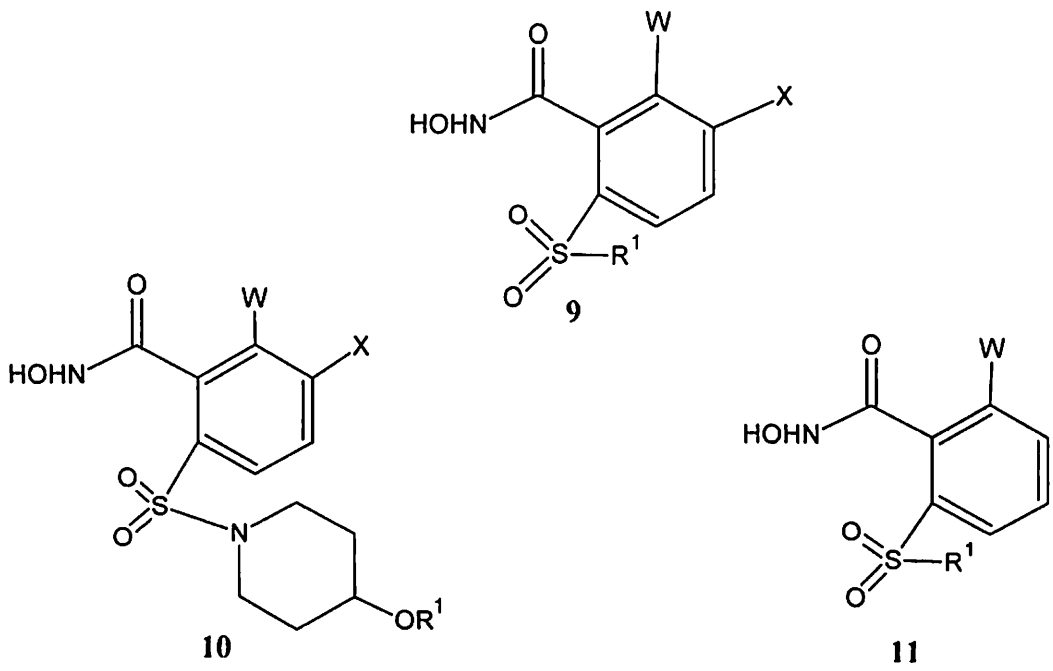
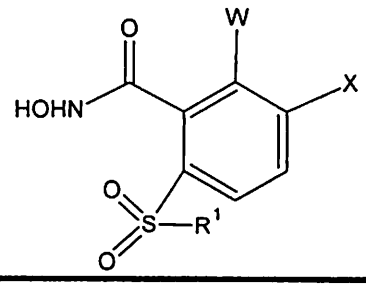


Figure 3.6. A series of piperidine sulfonamide aryl hydroxamic acid analogs

The complete series of **9** is listed in Table 3.33 along with their physicochemical properties that were found relevant in formulating QSAR for them. The most important physicochemical property that was found to be correlated with their activities was calculated hydrophobicity parameter ClogP. We tried to use several other properties, but they were found to be of no consequence. Rather some indicator variables were found to be useful which could account for the effects of some specific structural features in the compounds. These indicator variables are defined in the text as and when they appear. Table 3.34 lists the inhibition potencies of the compounds-observed as well as calculated from the correlations obtained-against MMP-2 and MMP-13 studied by Barta et al.

Table 3.33. A series of piperidine sulfonamide aryl hydroxamic acid analogs (9) and related physicochemical parameter(s).



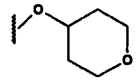
Compd	W	X	R^1	ClogP	I_I	I_{IN}
1	OCH_3	OCH_3	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.520	1	0
2	OCH_3	OCH_3	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-O-CF_3	2.590	1	0
3	OCH_3	OCH_3	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-2-O-CH_3	1.130	0	0
4	OCH_3	OCH_3	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-3-O-CH_3	1.480	0	0
5	OCH_3	OCH_3	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-O-CH_3	1.480	1	0
6	OCH_3	OCH_3	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_5	1.390	0	0
7	OCH_3	OCH_3	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-Cl	2.250	1	0
8	OCH_3	OCH_3	-(N[$(CH_2)_2$]$_2CH_2$)-O-piperonyl	1.430	0	0
9	-OCH_2O-		-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.970	1	0
10	-OCH_2O-		-(N[$(CH_2)_2$]$_2CH_2$)-O-piperonyl	1.810	0	0
11	-OCH_2CH_2O-		-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.930	1	0
12	F	H	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.670	1	0
13	Cl	H	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.820	1	0
14	$O(CH_2)_2$-O-CH_3	H	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.780	1	0
15		H	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.520	1	0
16	OCH_3	H	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.390	1	0
17	H	H	-NH-CH_2-C_6H_5	1.400	0	1
18	H	H	-NH-C_6H_4-4-O-CH_3	1.320	0	1
19	H	H	-(N[$(CH_2)_2$]$_2CH_2$)-CH_2-C_6H_5	2.940	0	0
20	H	H	-(N[$(CH_2)_2$]$_2CH_2$)-C_6H_5	2.410	0	0
21	H	H	-(N[$(CH_2)_2$]$_2CH_2$)-O-CH_2-C_6H_4-4-CF_3	2.360	0	0
22	H	H	-NH-C_6H_4-O-C_6H_5	2.400	0	1
23	H	H	-(N[$(CH_2)_3$]CH_2)-NH-C(O)-C_6H_4-4-OCH_3	1.080	0	1
24	H	H	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.870	1	0
25	H	H	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-OCF_3	2.940	1	0
26	H	H	-(N[$(CH_2)_3$]CH_2)-O-C_6H_4-4-CF_3	2.930	0	0
27	H	H	-(N[$(CH_2)_2$]$_2$N)-C(O)-C_6H_5	0.922	0	0
28	H	H	-(N[$(CH_2)_2$]$_2CH_2$)-O-C_6H_4-4-CF_3	2.670	1	0

Table 3.34. Observed and calculated MMP inhibition potencies of compounds of Table 3.33. Observed activities have been taken from ref. [26,27].

	log (1/IC_{50})					
	MMP-2			MMP-13		
Compd	Obsd	Calcd Eq. 47	Loo	Obsd	Calcd Eq. 48	Loo
1	8.62	9.05	9.10	8.57	8.43	8.41
2	9.10	8.98	8.96	8.43	8.33	8.32
3	6.48	6.71	6.79	5.60	5.75	5.78
4	7.92	7.12	6.88	6.60	6.44	6.40
5	8.74	9.10	9.24	7.85	8.30	8.47
6	8.96[a]	7.04	-	8.17[b]	6.29	-
7	9.52	9.25	9.18	8.82	8.67	8.64
8	9.00[a]	7.08	-	7.89[b]	6.36	-
9	8.52	8.43	8.41	7.74	7.59	7.55
10	8.96[a]	7.32	-	7.72	6.79	6.50
11	8.85	8.50	8.44	8.11	7.68	7.61
12	8.48	8.88	8.91	7.92	8.21	8.23
13	8.72	8.67	8.67	7.83	7.93	7.94
14	9.00	8.73	8.71	8.37	8.01	7.97
15	8.96	9.05	9.06	8.66	8.43	8.40
16	7.68[a]	8.88	-	6.96[b]	8.21	-
17	-	5.69	-	-	6.31	-
18	-	5.61	-	-	6.16	-
19	6.83	6.50	6.37	6.00	5.79	5.70
20	7.15	7.17	7.17	6.28[b]	6.70	-
21	7.46	7.21	7.12	6.05	6.68	6.80
22	5.46	5.82	6.42	5.05	6.73	6.94
23	5.64	5.27	4.68	5.66	5.62	5.60
24	8.89	8.60	8.56	7.55	7.82	7.85
25	8.70	8.48	8.44	7.48	7.66	7.69
26	5.74	6.52	6.84	5.70	5.82	5.86
27	6.00	6.35	6.66	5.17	5.18	5.18
28	8.48	8.88	8.91	7.91	8.21	8.23

[a]Not included in the derivation of Eq. 47.
[b]Not included in the derivation of Eq. 48.

The QSARs obtained for piperidine sulfonamide aryl hydroxamic acid analogs (**9**) were as follows:

MMP-2

$$\log (1/IC_{50}) = 3.528(\pm2.400)ClogP - 0.894(\pm0.592)(ClogP)^2 + 1.975(\pm0.458)I_1 - 1.352(\pm0.711)I_{1N} + 0.3.860(\pm2.162)$$

$$n = 22,\ r = 0.957,\ r^2_{cv} = 0.82,\ s = 0.42,\ F_{4,17} = 46.66(4.67),\ ClogP_o = 1.97 \qquad (47)$$

MMP-13

$$\log (1/IC_{50}) = 5.485(\pm2.130)ClogP - 1.334(\pm0.519)(ClogP)^2 + 1.866(\pm0.406)I_1 + 1.280(\pm1.945)$$

$$n = 22,\ r = 0.954,\ r^2_{cv} = 0.86,\ s = 0.38,\ F_{4,17} = 60.61(4.67),\ ClogP_o = 2.05 \qquad (48)$$

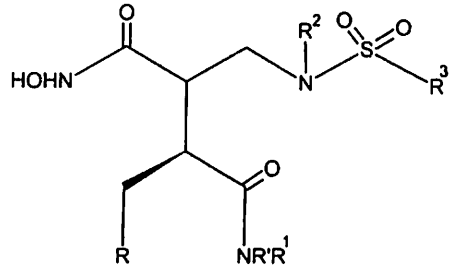
As obvious both Eqs. 47 and 48 express highly significant correlations between the inhibition potencies and the hydrophobic properties of the molecules. Both the equations are almost parallel and exhibit parabolic correlation in ClogP with an optimum ClogP equal to 1.97 for MMP-2 (Eq. 47) and 2.05 for MMP-13, which are almost identical. This similarity between the two equations lead to suggest that two enzymes (MMP-2 and MMP-13) interact with this series of compounds in a similar manner and that both involve the hydrophobic interaction predominantly. However, since in both the cases, the correlation is parabolic in ClogP, the highly hydrophobic molecules may not be conducive to the inhibition potencies. Since these inhibition potencies have been measured *in vitro*, where there is no intervening hydrophobic-lipophilic barrier, the decrease in the activity with the increase in ClogP value after the optimum value may be attributed to the steric effects of the molecules.

In both Eqs. 47 and 48, there is one common indicator variable I_1 which has been used for an R^1-subsititutent that contains a 4-substitued phenoxy piperidinyl moiety. For this substituent, I_1 is equal to 1 and for others it is zero. Now almost identical positive coefficient of this variable in both the equations suggests that the presence of such a moiety in R^1-substituent is equally conducive to both MMP-2 and MMP-13 inhibitions.

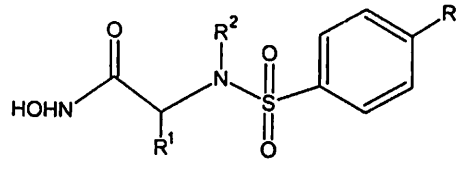
The only difference between the MMP-2 and MMP-13 inhibition is accounted for by the presence of additional parameter I_{IN} in Eq. 48. This parameter has been used for an R^1-substituent that contains an NH moiety (compounds 17, 18, 22, 23). The presence of this parameter with an negative coefficient in Eq. 47 suggests that an R^1-group with an NH moiety will be detrimental to the potency of the compound against MMP-2. This NH moiety can act as a hydrogen bond donor group, and the corresponding active site in the receptor may also probably be a hydrogen bond donor, requiring a hydrogen bond acceptor in the molecule, and this NH therefore would be undesirable. The absence of I_{IN} in Eq. 48 indicates that such a hydrogen bond site may not be present in MMP-3. Both Eqs. 47 and 48 represent highly significant correlations and have very high predictive value as in each case the value of r^2_{cv} is greater than 0.60.

3.7 Acyclic Hydroxamic Acid Analogs

The series of MMP inhibitors (**12-15**) taken for QSAR study have been reported by different research groups: **12** by Martin et al. [28]; **13** by Levin et al. [29]; **14** by Becker et al. [30]; and **15** by Venkatesan et al. [31] The similarity in all these series of compounds is the attachment of an acyclic moiety to the α-carbon of the hydroxamic acid. The derivatives of all **12** – **15** are listed in Tables 3.35 – 3.38, respectively, along with their relevant physiochemical properties that were found to be correlated with the MMP inhibition potencies. Correspondingly, Tables 3.39 – 3.42 display the inhibition potencies of compounds of Tables 3.35 – 3.38 with their observed as well as calculated values obtained from the correlations. In these tables, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. The most important physicochemical properties that were found to be correlated with the activities of the compounds were calculated hydrophobicity parameter (ClogP), polarizability (Pol), and molar volume (MV). Some indicator variables were also used to account for the effects of some specific structural features in the compounds. These variables are defined in the text as and when they appear.



12



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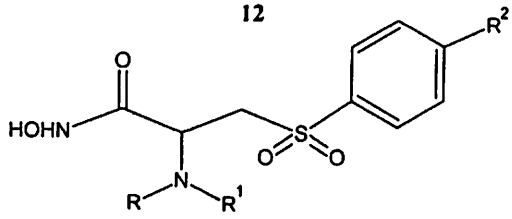

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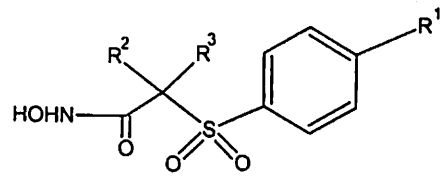
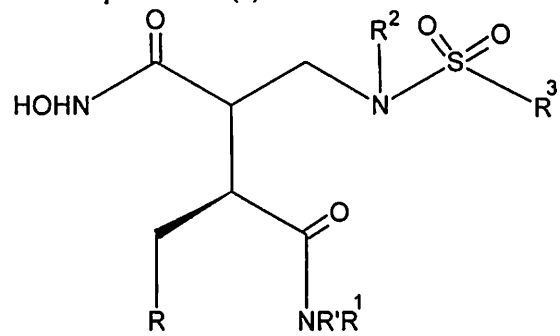


15

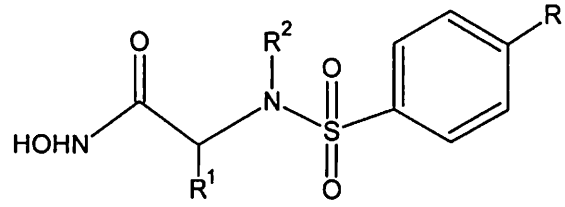
Figure 3.7. A series of acyclic hydroxamic acid analogs

Table 3.35. A series of acyclic hydroxamic acid analogs (**12**) and related physicochemical parameter(s).



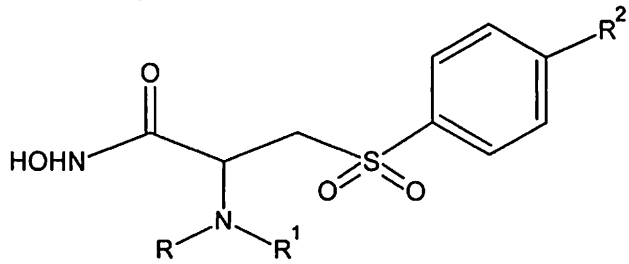
Compd	R	$NR'R^1$	R^3	R^2	ClogP	Pol	I_R	I_{R2}
1	iPr	piperidinyl	CH_3	CH_3	0.933	3.810	0	1
2	iPr	piperidinyl	CH_2CH_3	CH_3	1.462	4.000	0	1
3	iPr	piperidinyl	C_6H_4-4-OCH_3	CH_3	2.815	4.860	0	1
4	iPr	piperidinyl	dansyl	CH_3	4.214	5.820	0	1
5	iPr	$N(CH_3)_2$	CH_3	CH_3	0.044	3.340	0	1
6	c-pentyl	piperidinyl	CH_3	CH_3	1.038	3.910	1	1
7	c-pentyl	piperidinyl	CH_2CH_3	CH_3	1.567	4.090	1	1
8	c-pentyl	piperidinyl	C_6H_4-4-OCH_3	CH_3	3.449	5.140	1	1
9	c-pentyl	piperidinyl	dansyl	CH_3	4.848	6.110	1	1
10	c-pentyl	piperidinyl	naphthalyl	CH_3	3.925	5.400	1	1
11	c-pentyl	piperidinyl	CH_3	n-propyl	2.096	4.280	1	0
12	c-pentyl	piperidinyl	CH_3	c-pentyl	2.510	4.560	1	0
13	c-pentyl	piperidinyl	CH_3	c-propyl	1.622	4.190	1	0
14	c-pentyl	piperidinyl	CH_3	iPr	1.876	4.280	1	0
15	c-pentyl	piperidinyl	iPr	CH_3	1.876	4.280	1	1
16	c-pentyl	piperidinyl	C_6H_4-4-Cl	CH_3	3.464	4.900	1	1
17	c-pentyl	piperidinyl	$N(CH_3)_2$	CH_3	1.017	4.250	1	1
18	c-pentyl	piperidinyl	CF_3	CH_3	2.147	3.920	1	1
19	c-pentyl	morpholinyl	CH_3	CH_3	0.244	3.790	1	1
20	c-pentyl	morpholinyl	C_6H_4-4-OCH_3	CH_3	2.126	4.840	1	1

Table 3.36. A series of acyclic hydroxamic acid analogs (**13**) and related physicochemical parameter(s).



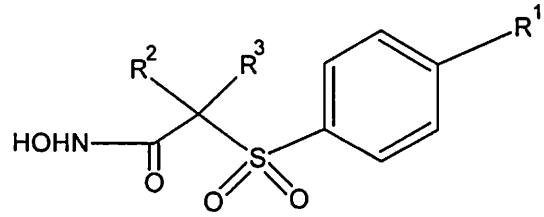
Compd	R	R^1	R^2	ClogP	I_{CC}	$I_{1,pyr}$	$I_{1,NH}$	$I_{2,H}$
1	OCH_2CCCH_3	H	H	0.861	1	0	0	1
2	OCH_2CCCH_3	H	CH_3	1.277	1	0	0	0
3	OCH_2CCCH_3	H	CH_2-3-pyridyl	1.484	1	0	0	0
4	OCH_2CCCH_3	CH_3	H	1.170	1	0	0	1
5	OCH_2CCCH_3	CH_3	CH_3	1.586	1	0	0	0
6	OCH_2CCCH_3	iPr	H	2.098	1	0	0	1
7	OCH_2CCCH_3	iPr	CH_3	2.514	1	0	0	0
8	OCH_2CCCH_3	tBu	H	2.497	1	0	0	1
9	OCH_2CCCH_3	$(CH_3)_2$	H	1.479	1	0	0	1
10	OCH_2CCCH_3	$CH(CH_3)OH$	H	0.467	1	0	0	1
11	OCH_2CCCH_3	CH_2SCH_2-3-pyridyl	H	1.969	1	1	0	1
12	OCH_2CCCH_3	CH_2SCH_2-3-pyridyl	CH_3	2.430	1	1	0	0
13	OCH_2CCCH_3	$C(CH_3)_2SCH_2$-3-pyridyl	H	2.677	1	1	0	1
14	OCH_2CCCH_3	$C(CH_3)_2SCH_2$-3-pyridyl	CH_3	3.138	1	1	0	0
15	OCH_2CCCH_3	C_6H_4-4-$O(CH_2)_2NHCH_3$	H	2.021	1	0	1	1
16	OCH_2CCCH_3	C_6H_4-4-$O(CH_2)_2NHCH_3$	CH_3	2.431	1	0	1	0
17	$NHCH_2CCH$	H	CH_3	1.778	0	0	0	0
18	SCH_2CCCH_3	H	CH_3	2.927	0	0	0	0
19	CH_2CH_2CN	H	CH_3	0.700	0	0	0	0

Table 3.37. A series of acyclic hydroxamic acid analogs (**14**) and related physicochemical parameter(s).



Compd	R	Config.	R^2	R^1	ClogP	MV	I	$I_{I,S}$	$I_{I,M}$
1	H		Ac	OCH_3	0.168	2.160	0	0	1
2	H		BOC	OCH_3	1.540	2.710	0	0	1
3	H		H	OCH_3	0.060	1.820	0	0	1
4	H		CbzGly	OCH_3	1.990	3.240	0	0	1
5	H		Ac	SC_6H_5	2.550	2.670	0	1	0
6	H		Cbz	SC_6H_5	4.740	3.320	0	1	0
7	H		Tos	SC_6H_5	4.620	3.310	0	1	0
8	H		H	SC_6H_5	2.440	2.330	0	1	0
9	H		CbzGly	SC_6H_5	4.370	3.740	0	1	0
10	H		Ac	OC_6H_5	2.310	2.590	0	0	0
11	H		Cbz	OC_6H_5	4.500	3.240	0	0	0
12	H		Tos	OC_6H_5	4.380	3.230	0	0	0
13	H	R	BOC	SC_6H_5	4.300	3.220	1	1	0
14	H	R	Ac	SC_6H_5	2.550	2.670	1	1	0
15	H	R	Cbz	SC_6H_5	4.740	3.320	1	1	0
16	H	R	BOC	OC_6H_5	4.060	3.140	1	0	0
17	H	R	isonicotinyl	OC_6H_5	2.740	3.010	1	0	0
18	H	R	2,6-dimethoxybenzoyl	OC_6H_5	3.940	3.450	1	0	0
19	CH_3	R	H	OC_6H_5	2.620	2.460	1	0	0
20	CH_3	R	Ac	OC_6H_5	2.810	2.740	1	0	0
21	CH_3	R	BOC	OC_6H_5	4.720	3.290	1	0	0
22	CH_3	R	4-pyridineacetyl	OC_6H_5	2.990	3.260	1	0	0
23	CH_3	R	$CH_2C_6H_5$	OC_6H_5	5.040	3.200	1	0	0

Table 3.38. A series of acyclic hydroxamic acid analogs (**15**) and related physicochemical parameter(s).



Compd	R^1	R^2	R^3	Pol	MV	I_1	$I_{2,ac}$	$I_{3,un}$	$I_{3,M}$	$I_{3,sp}$
1	OCH_3	$CH_2C_6H_5$	H	3.400	2.530	0	0	0	0	0
2	OCH_3	$CH_2C_6H_5$	CH_3	3.590	2.690	0	0	0	1	0
3	OCH_3	2-CH_2-naphthyl	H	4.100	2.870	0	0	0	0	0
4	OCH_3	2-CH_2-naphthyl	CH_3	4.280	3.030	0	0	0	1	0
5	OCH_3	4-CH_2-biphenyl	CH_3	4.570	3.340	0	0	0	1	0
6	OCH_3	isoprenyl	CH_3	3.320	2.630	0	0	0	1	0
7	OCH_3	isoprenyl	isoprenyl	4.030	3.170	0	0	1	0	0
8	OCH_3	allyl	allyl	3.320	2.640	0	0	0	0	0
9	OCH_3	CH_2CH=CH-C_6H_5	CH_3	3.950	2.940	0	0	0	1	0
10	OCH_3	n-propyl	n-propyl	3.340	2.740	0	0	0	0	0
11	OCH_3	Isopropyl	H	2.790	2.250	0	0	0	0	0
12	OCH_3	n-butyl	H	2.970	2.420	0	0	0	0	0
13	OCH_3	CH_2-cyclohexyl	CH_3	3.630	2.910	0	0	0	1	0
14	OCH_3	n-$C_{12}H_{25}$	H	4.440	3.740	0	0	0	0	0
15	OCH_3	propargyl	propargyl	3.170	2.420	0	0	0	0	0
16	OCH_3	3-picolyl	CH_3	3.500	2.620	0	1	0	1	0
17	OCH_3	3-picolyl	isoprenyl	4.210	3.170	0	1	1	0	0
18	OCH_3	3-picolyl	$CH_2CH(CH_3)_2$	4.050	3.120	0	1	0	0	0
19	OCH_3	3-picolyl	$(CH_2)_2CH(CH_3)_2$	4.230	3.290	0	1	0	0	0
20	OCH_3	3-picolyl	$(CH_2)_5CH_3$	4.050	3.120	0	1	0	0	0
21	OCH_3	3-picolyl	$(CH_2)_7CH_3$	4.600	3.610	0	1	0	0	0
22	OCH_3	3-picolyl	propargyl	3.780	2.790	0	1	0	0	0
23	OCH_3	CH_3	$(CH_2)_2$-piperidinyl	5.010	3.830	0	0	0	0	1
24	OCH_3	CH_3	$(CH_2)_2$-azepanyl	5.200	4.010	0	0	0	0	0
25	OCH_3	CH_3	$(CH_2)_2$-N[CH$(CH_3)_2]_2$	5.280	4.160	0	0	0	0	0
26	OCH_3	CH_3	$(CH_2)_2$-N$(CH_2CH_3)_2$	4.910	3.830	0	0	0	0	0
27	OCH_3	CH_3	$(CH_2)_3$-piperazinyl-4-C_6H_4-3-Cl	6.340	4.670	0	0	0	0	0
28	OCH_3	CH_3	$(CH_2)_2$-morpholinyl	4.900	3.740	0	0	0	0	0
29	OCH_2CH_3	CH_3	$(CH_2)_2$-N$(CH_2CH_3)_2$	5.090	3.990	0	0	0	0	0
30	O$(CH_2)_3CH_3$	CH_3	$(CH_2)_2$-piperidinyl	5.560	4.320	0	0	0	0	1
31	2-furyl	CH_3	$(CH_2)_2$-N[CH$(CH_3)_2]_2$	5.340	4.070	1	0	0	0	0
32	Br	CH_3	$(CH_2)_2$-N[CH$(CH_3)_2]_2$	5.000	3.750	1	0	0	0	0

Table 3.39. Observed and calculated MMP inhibition potencies of compounds of Table 3.35. Observed activities have been taken from ref. [28].

	log ($1/IC_{50}$)														
	MMP-1			MMP-2			MMP-3			MMP-8			MMP-13		
Compd	Obsd	Calcd Eq. 49	Loo	Obsd	Calcd Eq. 50	Loo	Obsd	Calcd Eq. 51	Loo	Obsd	Calcd Eq. 52	Loo	Obsd	Calcd Eq. 53	Loo
1	7.22	7.30	7.30	5.00[b]	5.73	-	5.40	5.51	5.57	7.00	7.08	7.12	-	6.20	-
2	7.30	7.19	7.13	5.70	5.85	5.91	5.70	5.67	5.66	7.00	7.16	7.23	-	6.30	-
3	7.10	7.13	7.16	6.22	6.41	6.48	6.40	6.37	6.36	7.70	7.53	7.47	7.00	6.73	6.34
4	8.22[a]	7.41	-	7.10	7.03	6.98	7.22	7.16	7.11	8.00	7.93	7.88	-	7.21	-
5	6.00[a]	7.58	-	5.70	5.42	5.24	-	5.13	-	5.40[c]	6.88	-	5.70	5.97	6.36
6	8.22	8.21	8.20	6.05	6.29	6.33	6.70	6.29	6.22	6.70[c]	7.90	-	6.40[d]	7.25	-
7	8.22	8.11	8.09	6.22	6.41	6.43	6.40	6.43	6.44	8.00	7.98	7.98	7.40	7.34	7.33
8	8.00	8.15	8.17	7.22	7.09	7.07	7.22	7.30	7.31	8.52	8.43	8.42	7.70	7.86	7.89
9	8.70	8.57	8.18	7.70	7.72	7.72	8.15	8.09	8.05	8.70	8.84	8.92	8.10	8.35	8.54
10	8.22	8.25	8.26	7.30	7.26	7.25	7.30	7.51	7.55	8.40	8.54	8.56	8.10	7.99	7.97
11	7.52	7.67	7.72	5.52	5.44	5.42	5.22	5.23	5.23	7.05	7.02	7.01	6.70	6.63	6.61
12	7.70	7.67	7.65	5.52	5.63	5.66	5.00	5.46	5.62	6.70	7.13	7.29	6.70	6.77	6.80
13	8.00	7.72	7.61	5.70	5.39	5.28	5.70	5.16	4.97	7.40	6.98	6.84	7.00	6.59	6.44
14	7.52	7.69	7.74	5.15	5.44	5.54	5.15	5.23	5.26	7.00	7.02	7.02	6.22	6.63	6.77
15	8.30	8.07	8.03	6.40	6.53	6.55	6.52	6.59	6.60	8.05	8.06	8.07	7.40	7.43	7.44
16	8.05	8.15	8.17	7.00	6.93	6.92	7.52	7.10	7.05	8.40	8.33	8.32	8.00	7.74	7.71
17	8.22	8.21	8.21	6.52	6.51	6.51	6.40	6.57	6.59	8.00	8.05	8.06	7.40	7.42	7.42
18	8.05	8.06	8.06	6.30	6.30	6.29	6.10	6.30	6.33	8.00	7.91	7.89	7.40	7.25	7.22
19	8.30	8.44	8.62	6.40	6.21	6.17	6.10	6.19	6.21	7.70	7.85	7.89	7.10	7.19	7.22
20	8.00	8.06	8.07	7.02	6.89	6.88	7.00	7.05	7.06	8.52	8.30	8.28	7.70	7.71	7.71

[a]Not included in the derivation of Eq. 49.
[b]Not included in the derivation of Eq. 50.
[c]Not included in the derivation of Eq. 52.
[d]Not included in the derivation of Eq. 53.

Table 3.40. Observed and calculated MMP inhibition potencies of compounds of Table 3.36. Observed activities have been taken from ref. [29].

	log (1/IC_{50})											
	MMP-1			MMP-9			MMP-13			TACE		
Compd	Obsd	Calcd Eq. 54	Loo	Obsd	Calcd Eq. 55	Loo	Obsd	Calcd Eq. 56	Loo	Obsd	Calcd Eq. 57	Loo
1	-	4.91	-	6.12	5.90	5.84	6.73	6.91	6.95	8.30	8.21	8.19
2	5.72	6.02	6.13	6.51	7.09	7.27	7.00	7.18	7.20	8.15	8.25	8.27
3	5.94	6.06	6.09	7.40	7.22	7.17	7.70	7.31	7.27	8.15	8.23	8.29
4	5.39	5.24	5.21	6.10	6.08	6.08	6.71	7.11	7.17	8.40	8.25	8.23
5	6.48	6.09	5.96	7.17	7.28	7.30	7.55	7.38	7.36	8.30	8.21	8.19
6	5.53	5.64	5.67	7.38[b]	6.65	-	7.74	7.71	7.70	8.00	7.97	7.96
7	6.59	6.92	6.99	7.96	7.85	7.82	7.42	7.97	8.06	7.82	7.64	7.59
8	6.06	6.11	6.12	6.65	6.89	6.97	7.39[c]	7.96	-	7.77	7.65	7.62
9	5.00	5.27	5.33	5.86	6.27	6.25	6.40[c]	7.31	-	7.89[d]	8.23	-
10	5.61	5.56	5.34	6.11	5.65	5.45	7.07	6.66	6.47	8.00	8.05	8.09
11	5.72	5.53	5.49	6.80	6.57	6.58	7.55	7.62	7.63	8.52	8.57	8.58
12	7.21	6.80	6.71	7.85	7.79	7.78	8.30	7.92	7.87	8.22	8.24	8.17
13	6.32	6.37	6.40	6.89	7.00	7.04	8.10	8.08	8.07	8.22	8.00	8.00
14	8.05	8.00	7.93	8.40	8.23	8.16	8.70	8.38	8.25	7.27	7.42	7.62
15	5.00	4.90	4.76	6.46	6.60	6.63	6.84[c]	7.66	-	7.74	8.02	8.05
16	6.03	6.13	6.26	7.96	7.79	7.77	7.57	7.92	7.97	7.59	7.71	7.74
17	-	3.65	-	5.82	6.04	6.29	6.12	6.23	6.36	8.10	8.14	8.14
18	5.31[a]	2.08	-	6.95	6.74	6.48	7.08	6.97	6.84	7.85[d]	7.17	-
19	-	5.13	-	7.13[b]	5.37	-	6.68[c]	5.54	-	8.15	8.16	8.16

[a]Not included in the derivation of Eq. 54.
[b]Not included in the derivation of Eq. 55.
[c]Not included in the derivation of Eq. 56.
[d]Not included in the derivation of Eq. 57.

Table 3.41. Observed and calculated MMP inhibition potencies of compounds of Table 3.37. Observed activities have been taken from ref. [30].

	log (1/IC$_{50}$)					
	MMP-13			MMP-1		
Compd	Obsd	Calcd Eq. 58	Loo	Obsd	Calcd Eq. 59	Loo
1	7.82	7.87	7.88	6.52	6.75	6.87
2	7.82	8.26	8.34	5.82[b]	6.96	-
3	7.82	7.83	7.84	6.60	6.61	6.63
4	-	7.90	-	7.40	7.16	6.71
5	8.23	8.06	8.02	-	4.97	-
6	8.43	8.69	8.78	-	5.19	-
7	9.40[a]	8.66	-	6.22[b]	5.19	-
8	7.62	8.03	8.14	-	4.81	-
9	9.10	8.58	8.43	-	5.36	-
10	8.96	8.48	8.40	6.11	6.12	6.12
11	8.96	9.11	9.16	5.85	6.33	6.40
12	9.22	9.07	9.02	6.40	6.33	6.32
13	8.40[a]	9.16	-	-	5.16	-
14	8.54	8.66	8.71	5.00	4.91	4.79
15	9.40	9.29	9.25	5.10	5.19	5.31
16	9.52	9.58	9.59	6.30	6.30	6.30
17	9.10	9.20	9.21	6.05	6.25	6.27
18	9.40	9.54	9.56	6.46	6.42	6.41
19	9.40	9.16	9.12	6.36	6.03	5.90
20	9.70	9.22	9.14	7.05[b]	6.16	-
21	9.52	9.77	9.82	5.80[b]	6.35	-
22	8.70[a]	9.27	-	6.59	6.34	6.31
23	9.70	9.86	9.90	6.32	6.32	6.32

[a]Not included in the derivation of Eq. 58.
[b]Not included in the derivation of Eq. 59.

Table 3.42. Observed and calculated MMP inhibition potencies of compounds of Table 3.38. Observed activities have been taken from ref. [31].

	log ($1/IC_{50}$)											
	MMP-1			MMP-9			MMP-13			TACE		
Compd	Obsd	Calcd Eq. 60	Loo	Obsd	Calcd Eq. 61	Loo	Obsd	Calcd Eq. 62	Loo	Obsd	Calcd Eq. 63	Loo
1	6.50	6.59	6.60	6.97	7.23	7.29	7.00	7.16	7.18	-	7.13	-
2	7.00[a]	6.57	-	7.96	7.93	7.93	7.96	7.79	7.76	-	6.99	-
3	6.23	6.50	6.52	6.71[b]	7.51	-	7.85	7.42	7.39	6.80	6.83	6.85
4	6.86[a]	6.48	-	8.10	8.21	8.24	8.05	8.04	8.04	-	6.69	-
5	6.80	6.44	6.42	7.64[b]	7.70	-	8.10	8.15	8.16	-	6.41	-
6	6.62	6.60	6.60	7.96	7.82	7.79	7.85	7.69	7.66	6.20[d]	7.04	-
7	7.60	7.39	7.12	9.30	8.94	8.48	9.40	8.93	8.46	6.09[d]	6.56	-
8	6.68	6.60	6.58	7.46	7.20	7.14	7.41	7.13	7.09	-	7.03	-
9	6.52	6.52	6.52	7.80	8.08	8.14	7.92	7.92	7.92	-	6.77	-
10	-	6.60	-	6.35[b]	7.21	-	6.85	7.14	7.17	-	6.94	-
11	6.19[a]	6.67	-	-	6.99	-	6.73	6.93	6.98	-	7.37	-
12	-	6.56	-	6.89	7.06	7.12	7.19	7.00	6.96	-	7.22	-
13	6.49	6.56	6.57	8.05	7.95	7.93	7.62	7.80	7.84	6.74	6.79	6.83
14	-	6.46	-	5.53[b]	7.65	-	6.50[c]	7.54	-	6.03	6.06	6.11
15	6.52	6.62	6.64	6.85	7.14	7.22	7.92[c]	7.07	-	-	7.22	-
16	6.59	6.24	6.16	7.42	7.29	7.23	7.66	7.76	7.77	-	7.05	-
17	6.81	7.02	7.29	8.05	8.41	8.86	8.52	8.99	9.47	6.69	6.57	6.53
18	6.00	6.17	6.19	7.20	6.89	6.81	7.89	7.40	7.33	-	6.61	-
19	6.24	6.14	6.13	6.92	6.96	6.97	7.05	7.47	7.49	-	6.46	-
20	5.94	6.17	6.21	-	6.89	-	6.90	7.40	7.43	6.12[d]	6.61	-
21	6.28	6.10	6.06	6.76	7.11	7.19	7.37	7.60	7.62	6.17	6.18	6.19
22	6.17	6.20	6.20	7.08	6.78	6.70	7.49	7.30	7.29	-	6.90	-
23	6.62	6.39	6.37	8.05	7.88	7.86	9.00	8.75	8.49	-	5.98	-
24	6.27	6.37	6.37	7.72	7.96	7.98	7.92	7.83	7.82	-	5.83	-
25	6.37	6.36	6.35	7.82	7.99	8.01	7.72	7.86	7.88	-	5.69	-
26	6.50	6.40	6.39	7.89	7.84	7.84	7.82	7.72	7.71	-	5.98	-
27	6.23	6.22	6.22	8.15	8.42	8.52	8.40	8.25	8.19	-	5.24	-
28	6.38	6.40	6.41	7.68	7.84	7.85	7.51	7.72	7.74	-	6.06	-
29	6.20	6.38	6.39	7.96	7.91	7.91	7.80	7.79	7.79	-	5.84	-
30	6.12	6.32	6.35	8.52	8.10	8.04	8.70	8.95	9.21	-	5.55	-
31	7.85	7.55	7.25	8.40	8.01	7.97	8.70[c]	7.87	-	-	5.77	-
32	7.29	7.59	7.90	7.24[b]	7.88	-	7.96	7.75	7.74	-	6.05	-

[a]Not included in the derivation of Eq. 60; [b]Not included in the derivation of Eq. 61.
[c]Not included in the derivation of Eq. 62; [d]Not included in the derivation of Eq. 63.

For the series of **12** (Table 3.35), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 7.600(\pm0.334) - 0.404(\pm0.263)ClogP + 0.085(\pm0.051)(ClogP)^2 + 0.935(\pm0.212)I_R + 0.388(\pm0.201)I_{R2}$$

$$n = 18,\ r = 0.954,\ r^2_{cv} = 0.75,\ s = 0.15,\ F_{4,13} = 32.80(5.20),\ ClogP_o = 2.38 \qquad (49)$$

MMP-2

$$\log (1/IC_{50}) = 0.648(\pm0.133)Pol + 0.496(\pm0.234)I_R + 1.088(\pm0.236)I_{R2} + 3.260(\pm0.633)$$

$$n = 19,\ r = 0.971,\ r^2_{cv} = 0.90,\ s = 0.19,\ F_{3,15} = 81.88(5.42) \qquad (50)$$

MMP-3

$$\log (1/IC_{50}) = 0.818(\pm0.195)Pol + 0.692(\pm0.324)I_R + 1.363(\pm0.328)I_{R2} + 2.398(\pm0.944)$$

$$n = 19,\ r = 0.963,\ r^2_{cv} = 0.89,\ s = 0.26,\ F_{3,15} = 64.04(5.42) \qquad (51)$$

MMP-8

$$\log (1/IC_{50}) = 0.425(\pm0.158)Pol + 0.783(\pm0.257)I_R + 1.045(\pm0.262)I_{R2} + 5.459(\pm0.762)$$

$$n = 18,\ r = 0.956,\ r^2_{cv} = 0.85,\ s = 0.20,\ F_{3,14} = 49.69(5.56) \qquad (52)$$

MMP-13

$$\log (1/IC_{50}) = 0.501(\pm0.212)Pol + 0.993(\pm0.424)I_R + 0.802(\pm0.319)I_{R2} + 4.296(\pm0.944)$$

$$n = 16,\ r = 0.947,\ r^2_{cv} = 0.72,\ s = 0.24,\ F_{3,12} = 34.55(5.95) \qquad (53)$$

All the above equations exhibit very significant correlations and present very interesting results. Equation (49) indicates that the inhibition potency of the compounds against MMP-1 will be largely controlled by the hydrophobic property of the molecules. It is shown that the activity will initially decrease with the increase in the ClogP value and then after ClogP attains an optimum value ($ClogP_o$ = 2.38), the activity will start increasing with the increase in the ClogP value.

Eqs. 50-53 obtained for four different MMP enzymes, MMP-2, MMP-3, MMP-8, and MMP-13, astonishingly express very parallel correlations, indicating that the inhibitions of all these four enzymes are primarily governed by the polarizability of the molecules. In all of Eqs. 50-53, the coefficients of polarizability factor (Pol) are almost identical. In all these Equations and also in Eq. 49, however, there are two indicator variables I_R and I_{R2}, which has been used for R- and R^2- substituents, respectively. I_R = 1 for R = c-pentyl, otherwise it is zero, similarly I_{R2} = 1 for $R^2 = CH_3$, otherwise it is zero. Now it is noticed that in all the five equations, both of these indicator variables have positive coefficients, indicating that a cyclopentyl group at R-position and a methyl group at R^2- position will be more conducive to the activity than any other group present at these positions (Table 3.35). It is also observed that the magnitude of the coefficient of each of these variables in Eqs. 50-53 is almost identical, hence each of the two structural features described by these variables is, just like polarizability, producing almost equal effects on the inhibition of the four MMPs of Eqs. 50-53. Almost equal effect is described of cyclopentyl group at R-position in MMP-1 inhibition (Eq. 49) but a slightly poor effect in it is shown of CH_3 group at R^2-position because of a very small coefficient of I_{R2}. A better effect of cyclopentyl group at R-position than an isopropyl group at this position (the only other substituent studied at this positon) in all the cases, however, can be attributed to its cyclic nature that might have better steric interaction. Similarly, a better effect of a CH_3 group at R^2-position than any other group at this position can be attributed to its small size, which may have better steric fit in the active site than any other group.

For the series of **13** (Table 3.36), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 6.869(\pm0.975) - 1.367(\pm1.068)ClogP + 0.551(\pm0.283)(ClogP)^2 - 0.673(\pm0.464)I_{1,N} - 0.785(\pm0.315)I_{2,H}$$

$$n = 15,\ r = 0.961,\ r^2_{cv} = 0.86,\ s = 0.27,\ F_{4,10} = 30.28(5.99),\ ClogP_o = 1.24 \qquad (54)$$

MMP-9

$$\log (1/IC_{50}) = 0.612(\pm0.222)ClogP + 1.363(\pm0.499)I_{CC} - 0.940(\pm0.337)I_{2,II} + 4.946(\pm0.682)$$

$$n = 17,\ r = 0.944,\ r^2_{cv} = 0.80,\ s = 0.29,\ F_{3,13} = 35.32(5.74) \quad (55)$$

MMP-13

$$\log (1/IC_{50}) = 0.644(\pm0.251)ClogP + 1.270(\pm0.556)I_{CC} + 5.085(\pm0.777)$$

$$n = 15,\ r = 0.890,\ r^2_{cv} = 0.68,\ s = 0.33,\ F_{2,12} = 22.90(6.93) \quad (56)$$

TACE

$$\log (1/IC_{50}) = 0.895(\pm0.492)ClogP - 0.368(\pm0.143)(ClogP)^2 + 0.525(\pm0.222)I_{1,pyr} + 7.708(\pm0.396)$$

$$n = 17,\ r = 0.910,\ r^2_{cv} = 0.71,\ s = 0.15,\ F_{3,13} = 20.89(5.74),\ ClogP_o = 1.22 \quad (57)$$

Now for this series of compounds also, Eq. 54 suggests that the hydrophobic property of the molecules will play a dominant role in MMP-1 inhibition. Since, like Eq. 49, Eq. 54 is also parabolic, the potency of the compounds will initially decrease and then after an optimum value of ClogP ($ClogP_o$ = 1.24) will start increasing as ClogP value increases. The two indicator variables $I_{1,N}$ and $I_{2,II}$ in Eq. 54, however, indicate the unwanted effects of two structural features in the molecule. $I_{1,N}$ stands with a value of unity for an R^1-substitutent which has an -NH- moiety, e.g., compounds 15 and 16 (Table 3.36), and for other it is zero and $I_{2,II}$ stands with a value of unity for an R^2-substitutent which is only H.

The negative effect of NH in R^1 can be attributed to the fact that NH is a hydrogen bond donor moiety and it must be facing in the receptor a site of the same nature, depriving the latter of the oppurtunity to form any hydrogen bond with the molecule (we may call it a hydrogen-bond repulsive interaction). The negative effect of H at R^2 establishes an optimum role played by a CH_3 group at this position. For the series of **12**, Eqs. 49-53 have shown that a CH_3 group at this position will invariably be more advantageous than a larger group at this position in the inhibiton of all the five enzymes.

Thus in the case of **13**, the negative effect of H at R^2, which is a much smaller group than CH_3, leads to the conclusion that a group of the size of CH_3 is an optimum requirement at this position (at the sulfonamide nitrogen).

The indicator variable $I_{2,11}$ is present in Eq. 55 also indicating the same preferential role of CH_3 at sulfonamide nitrogen in the inhibition of MMP-9 also as in the inhibition of MMP-1. Barring this variable, Eq. 55 seems to be similar to Eq. 56 obtained for MMP-13. In both Eqs. 55 and 56, the hydrophobic property of the molecules seems to be a major governing factor. Because of the similarity of the two equations, thus, both the MMP-9 and MMP-13 appear to involve the same inhibition mechanism with a dominance of hydrophobic interaction. In both Eqs. 55 and 56, there is however an additional indicator variable I_{CC} that stands with a value of unity for a butynyloxy substitutent at the aryl ring ($R = OCH_2CCCH_3$). A positive coefficent of it in both the Eqs. suggests that such a substitutent at the aryl ring would be of advantage for both MMP-9 and MMP-13 inhibitions. The beneficial role of this acetylene-derived linear substitutent may be assumed to be due to its ability to penetrate fully into any deep hydrophobic pocket of the receptor.

The hydrophobicity of the molecule is shown to govern the inhibition of TACE also (Eq. 57), but exactly in a reverse order of MMP-1 (Eq. 54). For both MMP-1 and TACE inhibitions the optimum value of ClogP is almost same, but while for the former it refers to a cut-off point from where the potency of the compounds starts decreasing, for the latter it refers to a cut-off point from where the potency starts increasing with the increase in the value of ClogP. An additional factor affecting the TACE inhibition is an R^1-substitutent that contains a pyridyl ring. Its effect is described by the indicator variable $I_{1,pyr}$,which has a value of unity for such a substitutent and is zero for others. A positive coefficient of it in Eq. 57 suggests that such an R^1-substituent will be beneficial to TACE inhibition. It may be beneficial because of its pyridine moiety that is cyclic in nature and contains a nitrogen with a lone pair of electrons. There can be steric effect of cyclic nature and an electronic effect of lone pair of electrons of nitrogen.

For the series of **14** (Table 3.37), the QSARs obtained were as follows:

MMP-13

$$\log (1/IC_{50}) = 0.287(\pm0.113)ClogP + 0.598(\pm0.334)I - 0.484(\pm0.344)I_{1,S} + 7.815(\pm0.366)$$

$$n = 19,\ r = 0.916,\ r^2_{cv} = 0.76,\ s = 0.31,\ F_{3,15} = 26.02(5.42) \qquad (58)$$

MMP-1

$$\log (1/IC_{50}) = 0.387(\pm0.363)MV + 0.827(\pm0.430)I_{1,M} - 1.175(\pm0.419)I_{1,S} + 5.080(\pm1.129)$$

$$n = 14,\ r = 0.939,\ r^2_{cv} = 0.72,\ s = 0.24,\ F_{3,10} = 24.70(6.55) \qquad (59)$$

The hydrophobic property of the molecules of this series also is found to be important for MMP-13 inhibition (Eq. 58) but not for MMP-1 (Eq. 59). For MMP-1, it is the molar volume that is shown to govern the activity, leading to the suggestion that compounds of this series involve van der Waals interaction with the receptors to inhibit MMP-1.

In both Eqs. 58 and 59, however, there are some indicator variables that account for the specific effects of some structural features of the compounds. The indicator variable that is common in both the equations is $I_{1,S}$ that stands with a value of unity for an R^1-substituent which is thiophenyl group. It is zero for other R^1-substituents. A negative coefficient of it in both the equations suggests that for the inhibition of both MMP-13 and MMP-1 a thiophenyl group at R^1-position will be less preferred than a methoxy or phenoxy group. For MMP-1, a methoxy group at R^1-position seems superior even to the phenoxy group. This is described by a variable $I_{1,M}$, which is equal to 1 for $R^1 = OCH_3$ and zero for R^1 = OPh / SPh. Similarly, the compounds having an R-configuration are shown to have better effect than other compounds for MMP-13 inhibition. It is described in Eq. 58 by the indicator variable I which has been used with a value of unity for such molecules.

For the series of **15** (Table 3.38), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 7.015(\pm0.515) - 0.125(\pm0.113)Pol - 0.342(\pm0.200)I_{2,pic} + 1.202(\pm0.331)I_{I} + 0.877(\pm0.321)I_{3,ipn}$$

$$n = 26,\ r = 0.909,\ r^2_{cv} = 0.61,\ s = 0.21,\ F_{4,21} = 24.87(4.31) \quad (60)$$

MMP-9

$$\log (1/IC_{50}) = 0.403(\pm0.148)Pol - 0.608(\pm0.277)I_{2,pic} + 1.456(\pm0.434)I_{3,ipn} + 0.625(\pm0.299)I_{3,M} + 5.861(\pm0.702)$$

$$n = 25,\ r = 0.912,\ r^2_{cv} = 0.64,\ s = 0.27,\ F_{4,20} = 24.80(4.43) \quad (61)$$

MMP-13

$$\log (1/IC_{50}) = 0.371(\pm0.148)Pol + 1.534(\pm0.448)I_{3,ipn} + 0.991(\pm0.470)I_{3,pip} + 0.560(\pm0.276)I_{3,M} + 5.896(\pm0.651)$$

$$n = 29,\ r = 0.903,\ r^2_{cv} = 0.63,\ s = 0.29,\ F_{4,24} = 26.37(4.22) \quad (62)$$

TACE

$$\log (1/IC_{50}) = 9.354(\pm1.083) - 0.881(\pm0.330)MV$$

$$n = 5,\ r = 0.980,\ r^2_{cv} = 0.74,\ s = 0.08,\ F_{1,3} = 71.87(21.20) \quad (63)$$

We have been invariably finding that QSARs obtained for MMP-9 and MMP-13 inhibitions by any class of compounds are very much similiar to each other. Equations 61 and 62 are very much in same line, exhibiting that the polarizability of this class of molecules would be a major controlling factor for both MMP-9 and MMP-13 inhibitions. The two other common factors that would affect the potency of these compounds against both the enzymes are two unique R^3-substituents, a CH_3 group and an isoprenyl group. The two indicator variables $I_{3,M}$ and $I_{3,ipn}$ of Eqs. 61 and 62 stand for only them with a value of 1 each, respectively. Almost identical positive coefficient of each of $I_{3,M}$ and $I_{3,ipn}$ in both the equations suggests that both these R^3-substituents are individually equally more beneficial to the inhibitions of both the enzymes than any other R^3-

substituent. The CH_3 may have its better effect because of its optimum steric size, and still better effect of isoprenyl group (the coefficient of $I_{3,ipn}$ is much larger than that of $I_{3,M}$ in both Eqs. 61 and 62) may be attributed to its linear chain nature, making it fully accessible to any deep hydrophobic pocket.

In Eq. 62, there is one more additional parameter $I_{3,pip}$ which describes a conducive effect of another R^3-substituent, i.e., $-(CH_2)_2$-piperidinyl, on MMP-13 inhibition. Its conducive effect may be probably because of nitrogen. Similarly, an additional parameter $I_{2,pic}$ is present in Eq. 61. It stands with a value of unity for a 3-picolyl group at R^2-position and because of its negative coefficient suggests a deterimental effect of such an R^2-substituent in the inhibition of MMP-9. For MMP-1 inhibition also, a 3-picolyl group at R^2-position is not shown to be conducive (Eq. 60). Probably this group is producing a steric effect at this postion. However, an isoprenyl group at R^3-position and a substituent other than an alkoxy group at R^1-position, whose effect is described by the indicator variable I_1, are found to be beneficial for MMP-1 inhibition. Polarizability of the molecules, on the other hand, is not favorable to the potency of the compounds.

For TACE inhibtion, the molecular volume is found to govern the activity (Eq. 63), but smaller would be the volume the better would be the activity. Since in this case we have used only five data points, the equation may not be very conclusive.

3.8 Piperazine, Piperidine and Diazepine Hydroxamic Acid Analogs

QSAR study has been carried out on different series of MMP inhibitors reported by the different research groups: **16** and **17** by Letavic et al. [32,33], **18** by Venkatesan et al. [34], and **19** by Levin et al. [35]. The derivatives of all **16-19** are listed in Tables 3.43 – 3.46, respectively, along with their relevant physiochemical properties that were found to be correlated with the MMP inhibition potencies. Tables 3.47 – 3.50 display the inhibition potencies of compounds of Tables 3.43 – 3.46, respectively, with their observed as well as calculated values obtained from the correlations. In these tables, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. The physicochemical parameters found to be useful in this QSAR study are the calculated hydrophobicity parameter (ClogP) and polarizability (Pol) of the whole molecules and the hydrophobic constant π of the substituents. Some indicator variables were also used to account for the effects of some specific structural features in the compounds. These variables are defined in the text as and when they appear.

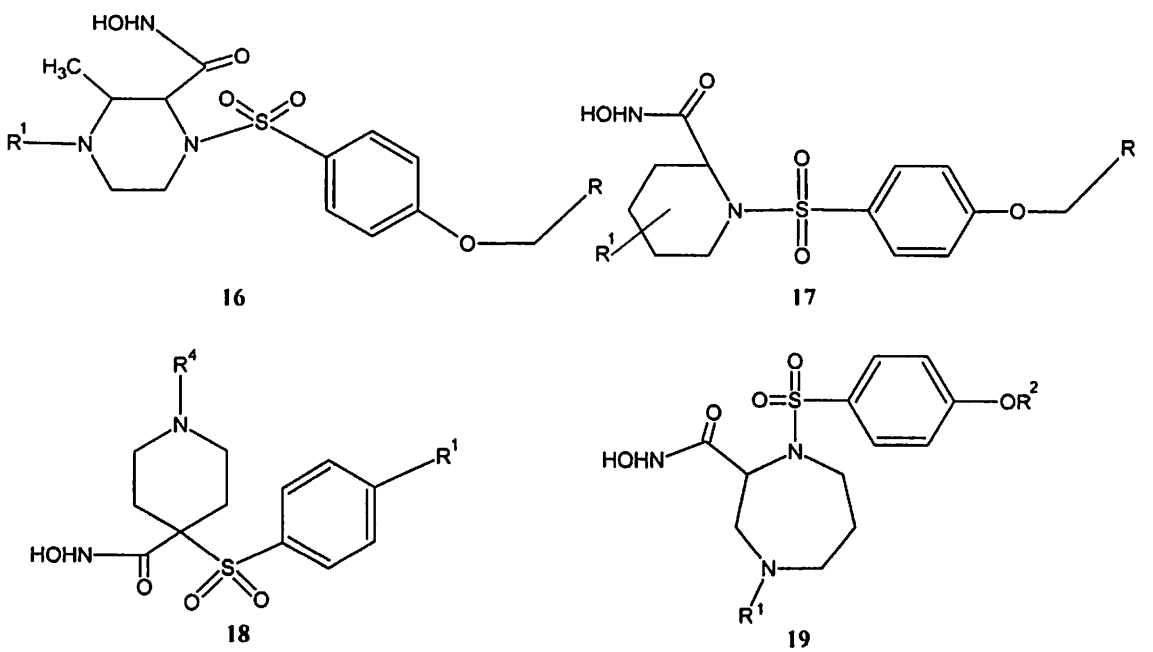
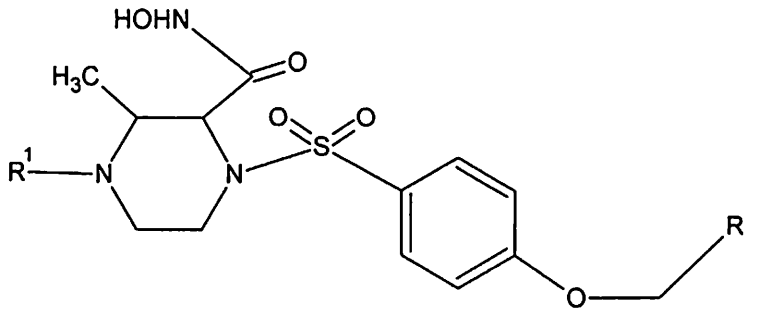


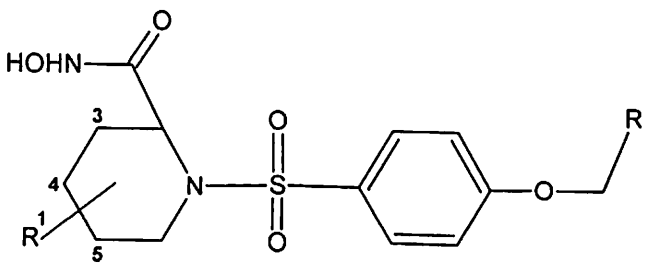
Figure 3.8. A series of piperazine, piperidine and diazepine hydroxamic acid analogs

Table 3.43. A series of piperazine hydroxamic acid analogs (**16**) and related physicochemical parameter(s).



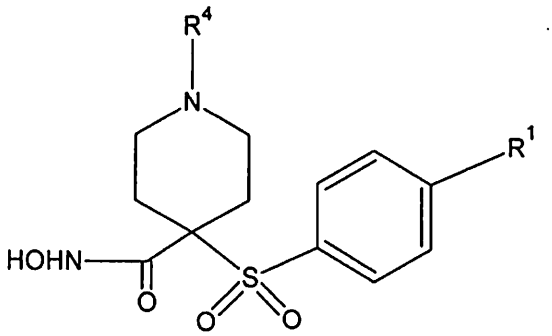
Compds	R	R^1	ClogP	$I_{I,II}$
1	C_6H_5	H	2.470	I
2	C_6H_4-2-CH_3	H	2.910	I
3	C_6H_4-2-CH_3	(O)CCH_3	2.580	0
4	C_6H_4-2-CH_2CH_3	(O)CCH_3	3.110	0
5	C_6H_3-3,5-$(F)_2$	(O)CCH_3	2.420	0
6	C_6H_4-4-F	(O)CCH_3	2.280	0
7	C_6H_3-2-CH_3,3-F	(O)CCH_3	2.730	0
8	C_6H_4-2-CF_3	(O)CCH_3	3.020	0
9	4-isoquinoline	(O)CCH_3	1.810	0
10	4-quinoline	(O)CCH_3	2.020	0
11	3-(2-CH_3)-pyridyl	(O)CCH_3	1.090	0
12	C_6H_4-2-CH_3	SO_2CH_3	2.980	0
13	C_6H_4-2-CH_3	$SO_2C_6H_4$-4-CH_3	5.120	0
14	C_6H_4-2-CH_3	CH_3	3.390	0
15	C_6H_4-2-CH_3	$CH_2C_6H_5$	5.220	0
16	C_6H_4-2-CH_3	(O)$CNHC_6H_5$	4.170	0
17	C_6H_4-2-CH_3	(O)$COCH_3$	3.670	0
18	C_6H_4-2-CH_3	(O)CNH-iPr	3.790	0
19	C_6H_4-2-CH_3	(O)$COCH_2CH_3$	4.200	0

Table 3.44. A series of piperidine hydroxamic acid analogs (**17**) and related physicochemical parameter(s).



Compd	R^1	R	$\pi_{X.R}$	I_{R1}	$I_{R.Ph}$	I_o
1	4-OH	C_6H_5	0.000	0	1	0
2	4-OH	C_6H_4-4-F	0.140	0	0	0
3	4-OH	C_6H_4-3-F	0.140	0	0	0
4	4-OH	C_6H_4-2-F	0.140	0	0	1
5	4-OH	C_6H_4-4-Cl	0.710	0	0	0
6	4-OH	C_6H_4-3-Cl	0.710	0	0	0
7	4-OH	C_6H_4-2-Cl	0.710	0	0	1
8	4-OH	C_6H_4-4-CH_3	0.560	0	0	0
9	4-OH	C_6H_4-3-CH_3	0.560	0	0	0
10	4-OH	C_6H_4-2-CH_3	0.560	0	0	1
11	4-OH	C_6H_4-3-OCH_3	-0.020	0	0	0
12	4-OH	C_6H_4-2-OCH_3	-0.020	0	0	1
13	4-OH	C_6H_4-2-CF_3	0.100	0	0	1
14	4-OH	C_6H_4-4-CN	-0.570	0	0	0
15	4-OH	C_6H_4-3-CN	-0.570	0	0	0
16	4-OH	C_6H_4-2-C_6H_5	1.960	0	0	1
17	5-OH	C_6H_5	0.000	1	1	0
18	5-OH	C_6H_4-4-CF_3	0.100	1	0	0
19	5-OH	C_6H_4-3-CF_3	0.100	1	0	0
20	5-OH	C_6H_4-2-CF_3	0.100	1	0	1
21	5-OH	C_6H_4-3-CN	-0.570	1	0	0
22	5-OH	C_6H_4-2-CN	-0.570	1	0	1
23	5-OH	C_6H_4-2-CH_3	0.560	1	0	1
24	5-OH	C_6H_4-2-CH_2CH_3	1.020	1	0	1
25	5-OH	C_6H_4-2-$CH(CH_3)_2$	1.530	1	0	1
26	5-OH	1-naphthyl	0.000	1	0	0
27	5-OH	C_6H_4-2-I	1.120	1	0	1

Table 3.45. A series of piperidine hydroxamic acid analogs (**18**) and related physicochemical parameter(s).

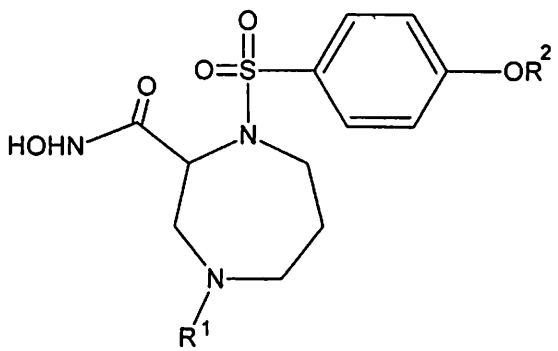


Compd	R^1	R^4	ClogP	Pol	$I_{1,OMe}$	$I_{1,PhCl}$	$I_{4,benz}$
1	$-OCH_3$	$CH_2C_6H_5$	1.260	4.210	1	0	1
2	$-OCH_3$	$CH_2C_6H_4$-3-OCH_3	1.179	4.460	1	0	1
3	$-OCH_3$	$CH_2C_6H_3$-3,4-$(Cl)_2$	2.566	4.590	1	0	1
4	$-OCH_3$	$CH_2C_6H_4$-4-CH_3	1.759	4.390	1	0	1
5	$-OCH_3$	2-CH_2-naphthyl	2.434	4.910	1	0	0
6	$-OCH_3$	4-CH_2-biphenyl	3.148	5.190	1	0	0
7	$-OCH_3$	Isoprene	1.510	3.940	1	0	0
8	$-OCH_3$	$CH_2C_6H_4$-4-Br	2.123	4.520	1	0	1
9	$-OCH_3$	3-Phenyl propyl	1.780	4.580	1	0	0
10	$-OCH_3$	tBu	0.539	3.780	1	0	0
11	$-OCH_3$	nBu	1.059	3.780	1	0	0
12	$-OCH_3$	Cyclo octyl	2.361	4.430	1	0	0
13	$-OCH_3$	CH_2CH_3	0.001	3.410	1	0	0
14	$-OCH_3$	iPr	0.140	3.600	1	0	0
15	$-OCH_3$	CH_3	-0.698	3.230	1	0	0
16	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_5$	2.847	4.760	0	0	1
17	$-OCH_3$	$CH_2C_6H_4$-4-F	1.403	4.220	1	0	1
18	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-4-F	2.990	4.770	0	0	1
19	$-OCH_3$	$CH_2C_6H_4$-4-OCH_3	1.179	4.460	1	0	1
20	$-OCH_3$	$CH_2CH_2C_6H_4$-4-OCH_3	1.490	4.650	1	0	0
21	$-OCH_3$	2-Phenyl ethyl	1.400	4.390	1	0	0
22	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-4-OCH_3	2.766	5.010	0	0	1
23	$-OCH_3$	3-Phenyloxy propyl	1.650	4.645	1	0	0
24	$-OCH_2CH_2CH_2CH_3$	3-Phenyloxy propyl	3.230	5.200	0	0	0
25	$-OCH_3$	2-Phenyloxy propyl	1.360	4.460	1	0	0
26	$-OCH_2CH_2CH_2CH_3$	2-Phenyloxy propyl	2.940	5.010	0	0	0
27	$-OCH_3$	$CH_2C_6H_4$-4-$O(CH_2)_2$-piperidinyl	2.513	5.640	1	0	1
28	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-4-$O(CH_2)_2$-piperidinyl	4.100	6.190	0	0	1
29	$-OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-3-$O(CH_2)_2$-morpholinyl	2.886	6.070	0	0	1
30	$-OCH_2CH_2CH_2CH_3$	CH_3	0.889	3.780	0	0	0
31	$-OCH_2CH_2CH_2CH_3$	CH_2CH_3	1.418	3.970	0	0	0
32	$-OCH_2CH_2CH_2CH_3$	nBu	2.476	4.330	0	0	0
33	$-OC_6H_4$-4-Cl	CH_3	1.938	4.220	0	1	0

Contd...

34	-OC_6H_4-4-Cl	CH_2CH_3	2.467	4.400	0	1	0
35	-OC_6H_4-4-Cl	nBu	3.525	4.770	0	1	0
36	-OC_6H_4-4-Cl	$CH_2C_6H_5$	3.726	5.200	0	1	1
37	-OC_6H_4-4-Cl	H	1.492	4.010	0	1	0
38	-$OCH_2CH_2CH(CH_3)_2$	$CH_2C_6H_5$	3.246	4.940	0	0	1
39	-$OCH_2CH(CH_3)_2$	$CH_2C_6H_5$	3.775	5.130	0	0	1
40	-$OCH_2CH_2CH_2CH_3$	$CH_2C_6H_4$-3-OCH_3	2.766	5.010	0	0	1
41	-OCH_3	$CH_2C_6H_4$-2-thiazolyl	3.004	5.120	1	0	1
42	-OCH_3	$CH_2C_6H_4$-2-pyridyl	1.861	5.100	1	0	1
43	-$OCH_2CH_2CH_2CH_3$	$CH_2C_6H_3$-3,4-$(Cl)_2$	2.847	4.760	0	0	1
44	-$OCH_2C_6H_5$	$CH_2C_6H_5$	3.028	5.190	0	0	1
45	-$OCH_2C_6H_4$-4-Cl	$CH_2C_6H_4$-4-CH_3	4.240	5.570	0	0	1
46	-2-furyl	$CH_2C_6H_5$	2.189	4.640	0	0	1
47	-OC_6H_4-4-Cl	$CH_2C_6H_4$-4-OCH_3	3.645	5.450	0	1	1

Table 3.46. A series of diazepine hydroxamic acid analogs (**19**) and related physicochemical parameter(s).



Compd	R^1	R^2	ClogP	$I_{1,COPh}$
1	$-CH_2C_6H_5$	CH_3	2.430	0
2	$-C(O)C_6H_5$	CH_3	1.220	1
3	$-C(O)C_6H_5$	C_6H_5	3.150	1
4	$-C(O)C_6H_4$-4-OCF_3	CH_3	2.550	0
5	$-C(O)C_6H_4$-2-C_6H_5	CH_3	3.110	0
6	$-C(O)CH_2NHBOC$	CH_3	1.600	0
7	$-C(O)CH_2NH_2$-HCl	CH_3	-0.690	0
8	-C(O)tBu	CH_3	0.790	0
9	-C(O)OtBu	CH_3	2.130	0
10	-H-HCl	CH_3	0.160	0
11	$-C(O)NHC_6H_5$	CH_3	1.260	0
12	$-C(O)NH(S)-CH_2CH_2C_6H_5$	CH_3	3.530	0

Table 3.47. Observed and calculated MMP and TACE inhibition potencies of compounds of Table 3.43. Observed activities have been taken from ref. [32].

	MMP-1			TACE		
Compd	Obsd	Calcd Eq. 64	Loo	Obsd	Calcd Eq. 65	Loo
1	4.92	4.91	4.91	7.60[b]	8.15	-
2	4.92	4.93	4.94	7.72[b]	8.02	-
3	5.80	5.93	5.95	8.22	8.12	8.10
4	5.17[a]	5.92	-	8.15	7.96	7.94
5	5.42[a]	5.92	-	8.22	8.16	8.16
6	5.77	5.89	5.92	8.22	8.21	8.20
7	5.72	5.94	5.98	8.15	8.07	8.06
8	5.00[a]	5.93	-	7.96	7.99	7.99
9	5.19[a]	5.77	-	-	8.35	-
10	6.08	5.84	5.78	-	8.28	-
11	5.47	5.44	5.33	8.30	8.56	8.71
12	5.89	5.93	5.94	8.22	8.00	7.98
13	-	5.00	-	7.49	7.36	7.31
14	-	5.88	-	7.51[b]	7.87	-
15	4.77	4.91	5.40	7.17	7.33	7.39
16	5.66	5.61	5.59	7.59	7.64	7.65
17	5.82	5.80	5.80	7.85	7.79	7.79
18	5.85	5.76	5.75	7.47	7.75	7.78
19	5.82	5.59	5.55	7.55	7.63	7.64

[a]Not included in the derivation of Eq. 64.
[b]Not included in the derivation of Eq. 65.

Table 3.48. Observed and calculated MMP and TACE inhibition potencies of compounds of Table 3.44. Observed activities have been taken from ref. [33].

	log (1/IC_{50})					
	MMP-1			TACE		
Compd	Obsd	Calcd Eq. 66	Loo	Obsd	Calcd Eq. 67	Loo
1	5.10	4.85	4.82	8.05	8.02	7.98
2	-	4.92	-	7.85	7.75	7.74
3	4.80	4.92	4.93	7.68	7.75	7.76
4	4.92	4.92	4.92	7.17[b]	7.93	-
5	5.20	5.22	5.23	8.15	7.90	7.85
6	5.19	5.22	5.23	8.00	7.90	7.88
7	4.54[a]	5.22	-	7.44[b]	8.08	-
8	4.52[a]	5.14	-	7.70	7.89	7.92
9	5.05	5.14	5.16	7.74	7.89	7.91
10	5.30	5.14	5.11	8.22	8.07	8.03
11	4.62	4.84	4.86	7.57	7.65	7.67
12	5.66[a]	4.84	-	7.85	7.83	7.83
13	-	4.84	-	7.80	7.91	7.95
14	4.52	4.55	4.56	7.60[b]	7.10	-
15	4.64	4.55	4.51	7.82[b]	7.89	-
16	-	5.88	-	7.17	7.21	7.34
17	4.52[a]	5.14	-	8.15	8.18	8.22
18	5.43	5.19	5.13	8.00	7.90	7.87
19	5.24	5.19	5.18	7.82	7.90	7.91
20	4.82	5.19	5.28	8.30	8.08	8.03
21	-	4.83	-	7.31	7.27	7.23
22	4.82	4.84	4.84	7.41	7.45	7.48
23	5.52	5.43	5.39	8.10	8.24	8.27
24	-	5.67	-	8.00	8.18	8.22
25	-	5.94	-	7.96	7.86	7.81
26	-	5.14	-	7.80	7.83	7.84
27	-	5.73	-	8.15	8.14	8.13

[a]Not included in the derivation of Eq. 66.
[b]Not included in the derivation of Eq. 67.

Table 3.49. Observed and calculated MMP and TACE inhibition potencies of compounds of Table 3.45. Observed activities have been taken from ref. [34].

	log ($1/IC_{50}$)											
	MMP-1			TACE			MMP-9			MMP-13		
Compd	Obsd	Calcd Eq. 68	Loo	Obsd	Calcd Eq. 69	Loo	Obsd	Calcd Eq. 70	Loo	Obsd	Calcd Eq. 71	Loo
1	6.31	6.08	6.07	6.64	6.68	6.69	8.00	7.63	7.61	8.70	8.43	8.41
2	6.28	6.06	6.05	6.67	6.59	6.57	8.05	7.58	7.56	8.70	8.39	8.38
3	6.35	6.27	6.26	6.94	6.75	6.70	8.22	8.18	8.18	8.70	8.67	8.67
4	6.31	6.19	6.19	6.65	6.72	6.73	7.77	7.89	7.90	8.70	8.57	8.57
5	6.43	6.26	6.25	6.77[b]	6.32	-	8.30	8.14	8.14	8.70	8.67	8.66
6	5.88	6.23	6.29	6.21	6.26	6.27	7.89	8.28	8.31	8.52	8.62	8.63
7	5.86	6.15	6.16	-	6.50	-	7.41	7.77	7.79	8.15	8.51	8.53
8	6.22	6.24	6.24	-	6.73	-	8.00	8.04	8.04	8.70	8.64	8.63
9	5.71[a]	6.20	-	6.30	6.35	6.36	7.89	7.90	7.90	7.96[d]	8.58	-
10	-	5.83	-	-	6.31	-	6.19[c]	7.14	-	6.83[d]	8.09	-
11	-	6.02	-	-	6.46	-	6.34[c]	7.51	-	7.42[d]	8.35	-
12	5.58	5.58	5.61	-	6.47	-	6.86[c]	8.12	-	7.54[d]	8.66	-
13	5.43	5.65	5.70	-	6.24	-	6.44	6.68	6.75	7.48	7.73	7.80
14	5.35[a]	6.26	-	-	6.23	-	6.43	6.81	6.88	7.47	7.83	7.90
15	5.29	5.16	4.99	-	6.00	-	6.32	5.98	5.59	7.36	7.16	6.93
16	5.62	5.67	5.67	6.81	6.70	6.68	8.40	8.24	8.23	9.00	8.92	8.91
17	6.18	6.12	6.12	6.60	6.71	6.73	7.80	7.71	7.71	8.70	8.48	8.46
18	5.33	5.66	5.68	-	6.70	-	7.72	8.26	8.29	8.30[d]	8.91	-
19	6.19	6.06	6.05	6.71	6.59	6.57	7.92	7.58	7.56	8.70	8.39	8.38
20	6.18	6.14	6.14	-	6.28	-	7.47	7.76	7.77	8.70	8.50	8.49
21	5.88	6.12	6.13	6.33	6.34	6.35	7.35	7.71	7.73	8.05	8.47	8.50
22	5.58	5.67	5.68	6.68	6.62	6.61	8.52	8.22	8.21	9.00	8.93	8.92
23	5.92	6.17	6.19	-	6.31	-	7.36	7.84	7.86	8.40	8.55	8.56
24	5.42	5.63	5.65	6.20	6.25	6.26	8.30	8.29	8.29	9.00	8.87	8.87
25	6.20	6.11	6.10	6.53	6.31	6.27	7.59	7.68	7.69	8.52	8.46	8.46
26	5.54	5.66	5.67	6.57[b]	6.31	-	8.30	8.25	8.25	8.70	8.91	8.93
27	6.41	6.26	6.25	6.41	6.42	6.42	8.52	8.16	8.15	8.52	8.67	8.68
28	5.71	5.44	5.36	6.24	6.18	6.15	8.70	8.27	8.16	9.00	8.60	8.51
29	5.66	5.67	5.67	6.30	6.30	6.30	8.70	8.25	8.22	8.70	8.92	8.93
30	5.47	5.38	5.36	6.23	6.41	6.51	8.00[c]	7.39	-	8.70	8.53	8.50
31	5.15	5.53	5.59	-	6.48	-	7.37	7.72	7.74	8.70	8.74	8.75
32	-	5.68	-	6.06	6.49	6.47	7.55[c]	8.15	-	8.70	8.93	8.95
33	5.85	5.63	5.61	6.57	6.49	6.51	8.70	8.74	8.75	8.70	8.87	8.90
34	5.76	5.67	5.67	6.38	6.37	6.32	9.00	8.92	8.90	9.00	8.93	8.93

Contd...

35	5.97	5.59	5.55	6.52	6.53	6.53	9.00	9.07	9.09	9.00	8.80	8.79
36	6.10[a]	5.55	-	6.52[b]	6.66	-	9.00	9.07	9.08	9.00	8.74	8.73
37	5.90	5.55	5.50	6.07[b]	6.11	-	8.70	8.53	8.48	8.70	8.77	8.78
38	5.59	5.63	5.64	6.25	6.62	6.63	8.40	8.29	8.29	8.70	8.87	8.88
39	5.50	5.53	5.53	-	6.54	-	7.85	8.30	8.35	8.30	8.73	8.78
40	5.82	5.67	5.66	6.57	6.59	6.60	8.52	8.22	8.21	9.00	8.93	8.92
41	6.27	6.25	6.24	6.56	6.52	6.51	7.96	8.26	8.28	8.52	8.64	8.66
42	6.37	6.21	6.20	6.53	6.57	6.58	8.22	7.93	7.92	8.70	8.60	8.59
43	5.44	5.67	5.68	-	6.62	-	7.70	8.24	8.26	8.30[d]	8.92	-
44	7.40[a]	5.66	-	6.38[b]	6.57	-	8.52	8.27	8.26	9.00	8.90	8.90
45	5.32	5.40	5.43	6.38	6.35	6.34	8.22	8.24	8.25	8.22	8.54	8.64
46	7.40[a]	5.66	-	6.38[b]	6.70	-	8.52	8.06	8.04	9.00	8.91	8.90
47	6.31[a]	5.57	-	6.31	6.46	6.48	9.00	9.07	9.09	9.00	8.77	8.74

[a]Not included in the derivation of Eq. 68.
[b]Not included in the derivation of Eq. 69.
[c]Not included in the derivation of Eq. 70.
[d]Not included in the derivation of Eq. 71.

Table 3.50. Observed and calculated MMP inhibition potencies of compounds of Table 3.46. Observed activities have been taken from ref. [35].

	MMP-9			MMP-13		
Compd	Obsd	Calcd Eq. 72	Loo	Obsd	Calcd Eq. 73	Loo
1	7.51[a]	7.22	-	7.19[b]	7.57	-
2	8.70	8.48	8.21	8.66	8.61	8.55
3	8.92	9.14	9.41	8.89	8.93	9.00
4	8.40	8.08	8.02	8.21	8.00	7.96
5	8.48	8.27	8.20	8.34	8.10	8.02
6	7.64	7.76	7.78	7.80	7.84	7.85
7	6.80	6.99	7.15	7.34	7.45	7.60
8	8.32[a]	7.22	-	7.96	7.70	7.65
9	8.04	7.94	7.92	7.59	7.93	7.98
10	7.22	7.27	7.29	8.29[b]	7.57	-
11	7.74	7.65	7.63	7.77	7.78	7.79
12	8.04	8.41	8.59	7.98	8.17	8.26

[a]Not included in the derivation of Eq. 72.
[b]Not included in the derivation of Eq. 73.

For the series of piperazine hydroxamic acid analogs **16** (Table 3.43), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 0.965(\pm0.473)ClogP - 0.173(\pm0.073)(ClogP)^2 - 1.008(\pm0.288)I_{1,H} + 4.593(\pm0.714)$$

$$n = 13,\ r = 0.947,\ r^2_{cv} = 0.67,\ s = 0.16,\ F_{3,9} = 26.16(6.99),\ ClogP_o = 2.79 \qquad (64)$$

TACE

$$\log (1/IC_{50}) = 8.888(\pm0.300) - 0.299(\pm0.086)ClogP$$

$$n = 14,\ r = 0.909,\ r^2_{cv} = 0.72,\ s = 0.16,\ F_{1,12} = 57.35(9.33) \qquad (65)$$

Equations 64 and 65 represent very significant correlations and suggest that the MMP-1 inhibition by this series of compounds will largely depend upon the hydrophobicity of the molecules. But since dependence of the potency of the compounds on the hydrophobic parameters ClogP is parabolic, the potency is optimized with an optimum value of ClogP equal to 2.79. For TACE inhibition, however, the potency of the compounds is shown to have a negative relation with the hydrophobicity of the molecules (Eq. 65). For MMP-1 inhibition, a negative effect is shown by R^1 = H, as described by $I_{1,H}$ parameter in Eq. 64. It means that a replacement of this hydrogen by any comparatively bulky group will be conducive to the activity, which may be because of some hydrophobic interaction of the group with any specific hydrophobic pocket of the receptor.

For the series of piperidine hydroxamic acid analogs **17** (Table 3.44), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 0.527(\pm0.234)\pi_{X,R} + 0.289(0.212)I_{R1} + 4.846(\pm0.128)$$

$$n = 15,\ r = 0.844,\ r^2_{cv} = 0.58,\ s = 0.17,\ F_{2,12} = 14.90(6.93) \qquad (66)$$

TACE

$$\log (1/IC_{50}) = 0.692(\pm0.197)\pi_{X,R} - 0.519(\pm0.132)(\pi_{X,R})^2 + 0.164(\pm0.130)I_{R1} + 0.351(\pm0.227)I_{R,Ph} + 0.181(\pm0.145)I_o + 7.667(\pm0.107)$$

$$n = 23,\ r = 0.909,\ r^2_{cv} = 0.72,\ s = 0.14,\ F_{5,17} = 16.21(4.34),\ (\pi_{X,R})_{opt} = 0.67 \qquad (67)$$

For this group of compounds, the MMP-1 inhibition is shown to be primarily governed by only the hydrophobic property of the substituents X present in the R-moiety of OCH_2R group of the aryl ring (Eq. 66). These substituents therefore seem to have specific hydrophobic interactions with the receptors. The additional factor to be favorable to the MMP-1 inhibition is the substitution of an OH group at the 5-position of piperidine ring (R^1 = 5-OH). The same at the 4-position would be less effective. This comparative effect of OH is described in Eq. 66 by the indicator variable I_{R1} with a value of 1 for R^1 = 5-OH and zero for R^1 = 4-OH. R^1 = 5-OH is shown to be favorable to the TACE inhibition also (Eq. 67). The hydrophobic property of X-substituents in R is also shown to be conducive to TACE inhibition, however till only $\pi_{X,R}$ attains an optimum value of 0.67. Two additional parameters, $I_{R,Ph}$ and I_o, describe the advantageous role of two discrete features of the molecules. $I_{R,Ph}$ stands with a value of 1 for R = C_6H_5 (i. e. unsubstituted phenyl moiety) and I_o stands with a value of 1 for 2-X (i.e., 2-position substituents at phenyl ring). Thus, de facto, an unsubstituted or a 2-substituted phenyl is indicated to be of additional advantage, but it is hard to explain as to how they would produce additional effects as compared to a 3-or 4-substituted phenyl.

For the series of another piperidine hydroxamic-acid analogs **18** (Table 3.45), the QSARs obtained were as follows:

MMP-1

$$\log (1/IC_{50}) = 0.532(\pm0.180)ClogP - 0.102(\pm0.044)(ClogP)^2 + 0.592(\pm0.170)I_{1,OMe} + 4.984(\pm0.249)$$

$$n = 38,\ r = 0.850,\ r^2_{cv} = 0.64,\ s = 0.21,\ F_{3,34} = 28.95(4.42),\ ClogP_o = 2.61 \qquad (68)$$

TACE

$$\log (1/IC_{50}) = 0.379(\pm0.282)ClogP - 0.064(\pm0.054)(ClogP)^2 - 0.306(\pm0.140)Pol + 0.312(\pm0.108)I_{4,benz} + 7.283(\pm0.576)$$

$$n = 27,\ r = 0.840,\ r^2_{cv} = 0.55,\ s = 0.11,\ F_{4,22} = 12.91(4.31),\ ClogP_o = 2.96 \quad (69)$$

MMP-9

$$\log (1/IC_{50}) = 0.909(\pm0.263)ClogP - 0.128(\pm0.061)(ClogP)^2 + 0.770(\pm0.285)I_{1,PhCl} + 6.686(\pm0.284)$$

$$n = 42,\ r = 0.891,\ r^2_{cv} = 0.74,\ s = 0.31,\ F_{3,38} = 48.79(4.34),\ ClogP_o = 3.55 \quad (70)$$

MMP-13

$$\log (1/IC_{50}) = 0.726(\pm0.192)ClogP - 0.141(\pm0.045)(ClogP)^2 - 0.265(\pm0.177)I_{1,OMe} + 8.000(\pm0.265)$$

$$n = 41,\ r = 0.850,\ r^2_{cv} = 0.63,\ s = 0.23,\ F_{3,37} = 31.90(4.36),\ ClogP_o = 2.57 \quad (71)$$

It is to be noted that as for piperidine hydroxamic acids **17**, for piperidine hydroxamic acids **18** also MMP-1 and TACE inhibitions are controlled by the hydrophobic property of the molecules (Eqs. 68 and 69). In this case, however, there exists a better similarity between the QSARs of MMP-1 and TACE. For both, there exists a parabolic dependence of the inhibition potency of the compounds on ClogP and for both the optimum value of ClogP ($ClogP_o$) is almost same. However, for the TACE inhibition, the polarizability of the molecules is also found to play a role and, as obvious from Eq. 69, it is producing an adverse effect. It is of course in line with the fact that polarizability will always play an opposite role to that of hydrophobicity.

For the series of **18**, the hydrophobicity of the molecules is shown to govern also the activity of the compounds studied against two other MMPs, MMP-9 and MMP-13 (Eqs. 70 and 71). The parabolic dependence of the activity on ClogP in these two cases also leads to suggest that in the inhibition of all the four MMPs here, the hydrophobicity of the molecules plays almost an identical role. However, in all the cases, there are some indicator variables describing the positive or negative effect of some typical substituents.

In the case of MMP-1 and MMP-13 (Eqs. 68 and 71), the variable $I_{1,OMe}$ describes the effect of a methoxy group substituted at the aryl ring (R^1 = OMe). It has a value of 1 for R^1 = OMe and zero for R^1 being any other substitutent. Now while a positive coefficient of $I_{1,OMe}$ in Eq. 68 indicates a favorable role of an OMe group at R^1-position in MMP-1 inhibition, for MMP-13 inhibition a negative coefficient of it in Eq. 71 indicates a detrimental effect of OMe. The one possible reason of this difference may be the size of this substitutent. The methoxy substitutent is the smallest one among all R^1-substituents. A favorable role of it, as compared to other substituents, in MMP-1 may be due to its optimum steric fit with the receptor site in this enzyme and its comparative unfavorable role in MMP-13 may be due to its insufficiently small size to have any interaction with the receptor site in this enzyme.

In Eq. 70, $I_{1,PhCl}$ stands with a value of unity for R^1 = OC_6H_4-4-Cl. A positive coefficient of it exhibits a favorable role of this substituent for MMP-9 inhibition. Here the chlorine may be expected to have some electronic interaction with the receptor. Similarly, in Eq. 69 $I_{4,benz}$ describes a conducive role of a substituted or unsubstituted benzyl present at the piperidine nitrogen (R^4-substituent). This variable has a value of 1 for R^4 = $CH_2C_6H_4$-X and zero for any other R^4-substituent.

For the series of diazepine hydroxamic acid analogs **19** (Table 3.46), the QSARs obtained were as follows:

MMP-9

$$\log (1/IC_{50}) = 0.339(\pm0.148)ClogP + 0.853(\pm0.479)I_{1,COPh} + 7.217(\pm0.329)$$
$$n = 10,\ r = 0.942,\ r^2_{cv} = 0.70,\ s = 0.25,\ F_{2,7} = 27.51(9.55) \qquad (72)$$

MMP-13

$$\log (1/IC_{50}) = 0.168(\pm0.135)ClogP + 0.834(\pm0.415)I_{1,COPh} + 7.574(\pm0.304)$$
$$n = 10,\ r = 0.914,\ r^2_{cv} = 0.71,\ s = 0.22,\ F_{2,7} = 17.75(9.55) \qquad (73)$$

For most of the cases, the correlation obtained for MMP-9 and MMP-13 have been found to be parallel. We observe the same for the series of **19**, too (Eqs. 72 and 73). Equations 72 and 73 clearly exhibit that for both these MMPs, the hydrophobicity of the molecules of this series of compounds will be a dominant factor and that a benzoyl group at the diazepine nitrogen ($R^1 = C(O)C_6H_5$) would be an additional advantage as described by the indicator variable $I_{1,COPh}$. The hydrophobicity of the molecules will obviously lead to a hydrophobic interaction of the molecules with the enzymes and the benzoyl group at the nitrogen may have some optimum polar interaction with some sites of the receptor.

3.9 Benzodiazepine Hydroxamic Acid Analogs

The series of benzodiazepine hydroxamic acid analogs **20** and **21** were reported by Nelson et al. [36] and Levin et al. [37] were listed in Tables 3.51 – 3.52, respectively, along with the physicochemical parameters that were found to be correlated with their MMP/TACE inhibition potencies. Their inhibition potencies, observed as well as calculated from correlations obtained, are listed in Tables 3.53 and 3.54, respectively. In these Tables, IC_{50} refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. The parameters that have been used here are calculated hydrophobicity (ClogP) and E-State index (S) of nitrogen atom attached to sulfonyl group. Some indicator variables were also used to account for the effects of some specific structural features in the compounds. These variables are defined in the text as and when they appear.

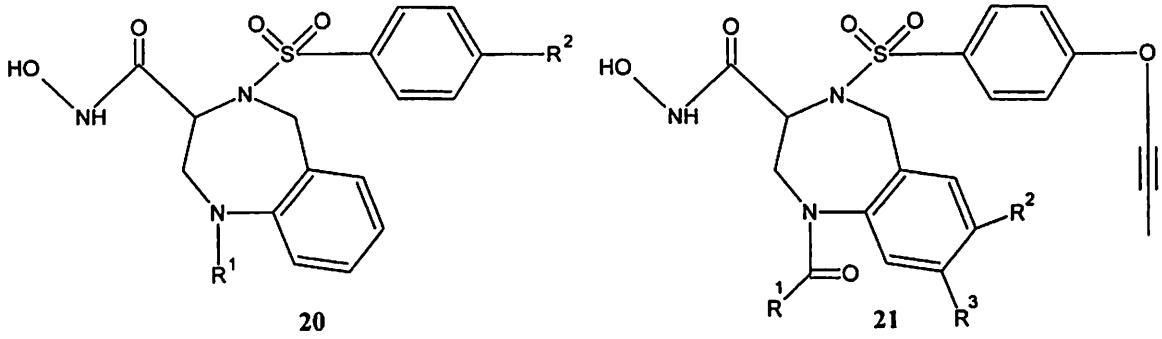
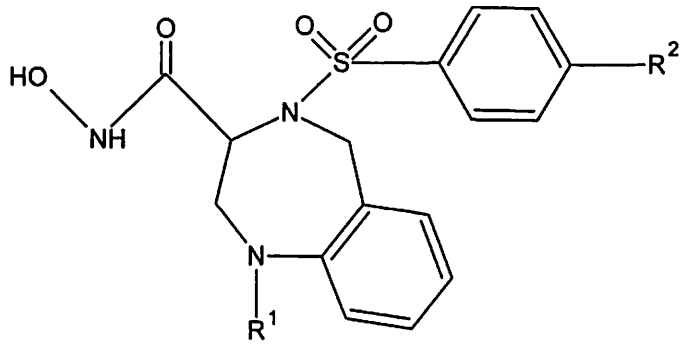
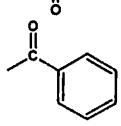
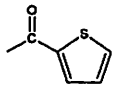
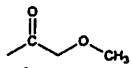
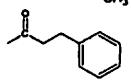
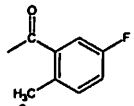
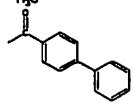
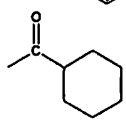
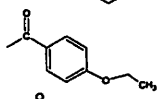
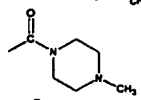
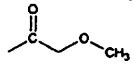
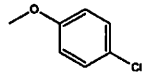


Figure 3.9. A series of benzodiazepine hydroxamic acid analogs

Table 3.51. A series of benzodiazepine hydroxamic acid inhibitors (**20**) and related physiochemical parameters.



Compd	R^1	R^2	ClogP	S_N	$I_{R1\text{-}A}$	$I_{R2\text{-}CC}$	I_{AC}
1		—OCH$_3$	1.370	-19.266	0	0	0
2		—OCH$_3$	1.297	-23.512	0	0	0
3		—OCH$_3$	2.595	-18.936	1	0	0
4		—OCH$_3$	1.954	-17.596	0	0	1
5		—OCH$_3$	2.372	-18.769	1	0	0
6		—OCH$_3$	1.424	-20.266	0	0	0
7		—OCH$_3$	3.467	-17.936	1	0	0
8		—OCH$_3$	3.313	-24.276	1	0	0
9		—OCH$_3$	4.483	-18.276	1	0	0
10		—OCH$_3$	3.401	-16.436	0	0	1
11		—OCH$_3$	3.344	-19.606	1	0	0
12		—OCH$_3$	2.555	-16.766	0	0	1
13			1.424	-21.717	0	0	0

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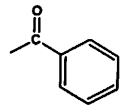
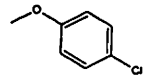
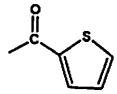
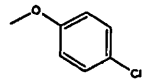
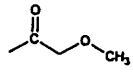
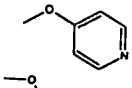
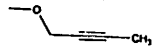
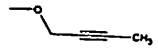
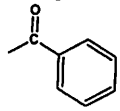
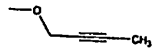
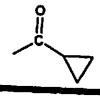
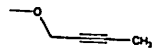
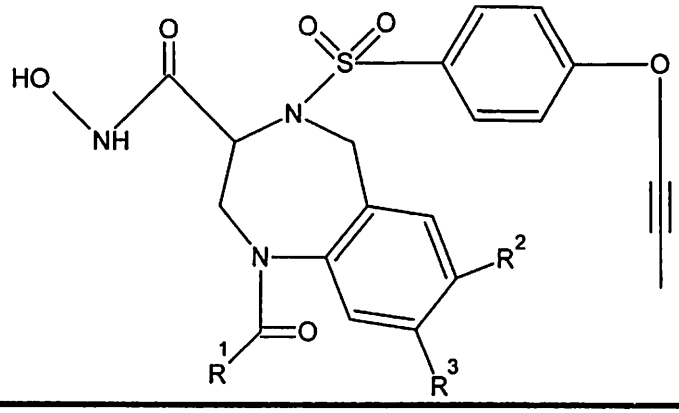
14			2.595	-20.387	1	0	0
15			1.424	-22.498	1	0	0
16			1.424	-20.936	0	0	0
17			2.499	-19.766	0	1	0
18			2.426	-24.012	0	1	0
19			3.724	-19.436	1	1	0
20			3.083	-18.096	0	1	1

Table 3.52. A series of benzodiazepine hydroxamic acid inhibitors (**21**) and related physiochemical parameters.



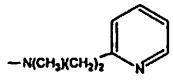
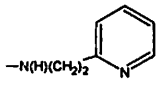
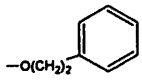
Compd	R_1	R_2	R_3	ClogP	S_N	$I_{R1\text{-}A}$	$I_{R2\text{-}H}$
1	—CH_3	—H	—H	2.499	-19.106	0	0
2	—CH_2OCH_3	—H	—H	2.499	-23.606	0	0
3		—H	—H	2.900	-20.276	1	0
4		—H	—H	2.623	-19.776	1	0
5		—H	—H	1.668	-20.776	1	0
6	—CH_3	—$N(CH_3)_2$	—H	2.664	-19.106	0	1
7	—CH_3	—$N[(CH_2)_2]_2O$	—H	1.955	-18.606	0	1
8	—CH_3	—$N[(CH_2)_2]_2NCH_3$	—H	2.397	-17.106	0	1
9	—CH_3		—H	3.264	-18.776	0	1
10	—CH_3		—H	2.598	-19.276	0	1
11	—CH_3		—H	4.515	-19.276	0	1
12	—CH_3	—H	—CH_2OH	1.461	-21.606	0	0
13	—CH_3	—H	—CH_2NHCH_3	1.867	-19.106	0	0
14	—CH_3	—H	—$CH_2N(CH_3)_2$	2.333	-18.606	0	0
15	—CH_3	—H	—$CH_2N[(CH_2)]_2NH$	2.232	-17.606	0	0
16	—CH_3	—H	—$CH_2NHCOCH_3$	1.307	-23.776	0	0
17	—CH_3	—H	—$CONHCH_3$	1.518	-24.276	0	0

Table 3.53. Observed and calculated MMP and TACE inhibition potencies of compounds of Table 3.51. Observed activities taken from ref. [36].

	log ($1/IC_{50}$)											
	MMP-1			TACE			MMP-9			MMP-13		
Compd	Obsd	Calcd Eq. 74	Loo	Obsd	Calcd Eq. 75	Loo	Obsd	Calcd Eq. 76	Loo	Obsd	Calcd Eq. 77	Loo
1	7.74	7.48	7.35	6.99	6.96	6.95	8.85	8.88	8.88	9.00	8.98	8.97
2	6.80[a]	7.57	-	6.98	6.97	6.97	8.10	8.38	8.45	8.52	8.49	8.49
3	7.80	7.49	7.43	7.02	6.80	6.78	9.22	8.92	8.87	9.40	9.02	8.95
4	6.77	6.85	6.86	7.16	6.88	6.85	8.40	8.28	8.20	8.52	8.34	8.22
5	7.70	7.64	7.62	7.89[b]	6.83	-	9.00	8.94	8.93	9.00	9.04	9.05
6	7.47	7.41	7.39	7.02	6.96	6.94	8.70	8.76	8.77	8.70	8.87	8.88
7	6.28[a]	7.18	-	6.68	6.68	6.68	7.74[c]	9.03	-	7.59[d]	9.14	-
8	7.26	7.20	7.19	6.57	6.70	6.72	8.40	8.29	8.24	8.70	8.40	8.24
9	7.28	7.31	7.43	6.70	6.55	6.46	9.15	9.00	8.96	9.40	9.10	9.02
10	6.33	6.06	5.94	6.50	6.69	6.72	7.89	8.42	8.74	8.15	8.47	8.68
11	7.62	7.20	7.13	6.80	6.70	6.68	8.70	8.84	8.86	8.70	8.94	8.97
12	5.30[a]	6.40	-	6.09[b]	6.80	-	6.73[c]	9.17	-	6.50[d]	9.28	-
13	7.21	7.41	7.49	6.80	6.96	6.98	8.70	8.59	8.58	8.70	8.70	8.71
14	7.23	7.49	7.55	6.28[b]	6.80	-	8.70	8.75	8.75	8.70	8.85	8.87
15	7.46	7.64	7.68	6.60	6.83	6.85	8.70	8.50	8.46	8.40	8.61	8.64
16	6.12[a]	7.41	-	6.80	6.96	6.98	8.70	8.68	8.68	8.70	8.79	8.80
17	6.08	6.43	6.51	7.80	7.74	7.72	6.64[c]	7.67	-	7.11[d]	8.05	-
18	6.59	6.48	6.45	7.70	7.75	7.77	7.02	7.17	7.29	7.46	7.55	7.63
19	6.78	7.16	7.24	7.23	7.58	7.72	7.45	7.71	7.95	8.02	8.08	8.13
20	6.08	6.14	6.17	8.00	7.66	7.55	7.48	7.07	6.63	7.54	7.40	7.23

[a]Not included in the derivation of Eq. 74.
[b]Not included in the derivation of Eq. 75.
[c]Not included in the derivation of Eq. 76.
[d]Not included in the derivation of Eq. 77.

Table 3.54. Observed and calculated MMP and TACE inhibition potencies of compounds of Table 3.52. Observed activities taken from ref. [37].

	log ($1/IC_{50}$)					
	MMP-1			TACE		
Compd	Obsd	Calcd Eq. 78	Loo	Obsd	Calcd Eq. 79	Loo
1	6.08	6.08	6.08	7.80	7.80	7.80
2	6.07	6.12	6.13	7.09	7.43	7.53
3	6.90	6.88	6.84	7.48	6.82	7.11
4	6.62	6.61	6.61	7.05	7.23	7.39
5	6.45	6.48	6.53	7.16	7.27	7.20
6	6.17	6.20	6.22	6.71	7.19	6.88
7	5.90	5.95	5.96	6.89	6.83	6.87
8	6.07	6.03	6.01	7.04	6.87	6.98
9	-	6.95	-	6.92	6.99	6.84
10	-	6.15	-	7.31[d]	6.82	-
11	-	10.06	-	7.44[d]	6.85	-
12	6.30	6.17	6.12	7.92	7.59	7.54
13	6.34[a]	5.96	-	7.85	7.80	7.78
14	6.04	6.00	5.99	7.74	7.84	7.87
15	6.32[a]	5.97	-	7.85	7.92	7.96
16	6.24	6.30	6.38	7.51	7.41	7.39
17	6.09	6.12	6.13	7.39	7.37	7.36

[a]Not included in the derivation of Eq. 78.
[b]Not included in the derivation of Eq. 79.

The following are the QSAR obtained for series **20** (Table 3.51)

MMP-1

$$\log(1/IC_{50}) = 1.123(\pm0.347)I_{R1\text{-}A} - 1.929(\pm0.972)ClogP + 0.259(\pm0.170)(ClogP)^2 + 9.635(\pm1.276)$$

$$n = 16,\ r = 0.911,\ r^2_{cv} = 0.72,\ s = 0.27,\ F_{3,12} = 19.55(5.95),\ ClogP_o = 3.72 \quad (74)$$

TACE

$$\log(1/IC_{50}) = 0.930(\pm0.251)I_{R2\text{-}CC} - 0.133(\pm0.112)ClogP + 7.143(\pm0.299)$$

$$n = 17,\ r = 0.906,\ r^2_{cv} = 0.71,\ s = 0.20,\ F_{2,14} = 31.97(6.51) \quad (75)$$

MMP-9

$$\log(1/IC_{50}) = 0.119(\pm0.074)S_N - 1.149(\pm0.355)I_{R2\text{-}CC} - 0.798(\pm0.440)I_{AC} + 11.169(\pm1.535)$$

$$n = 17,\ r = 0.932,\ r^2_{cv} = 0.65,\ s = 0.25,\ F_{3,14} = 28.47(5.56) \quad (76)$$

MMP-13

$$\log(1/IC_{50}) = 0.115(\pm0.065)S_N - 0.885(\pm0.314)I_{R2\text{-}CC} - 0.834(\pm0.390)I_{AC} + 11.205(\pm1.361)$$

$$n = 17,\ r = 0.927,\ r^2_{cv} = 0.73,\ s = 0.23,\ F_{3,14} = 26.34(5.56) \quad (77)$$

Equation (74) shows the existence of parabolic relationship between logP and the inhibitory activities of the compounds for the MMP-1, suggesting that activity would initially decrease with increase in logP and then would start increasing after the logP reaches an optimum value ($ClogP_o$) which is 3.72 for MMP-1.

In Eq. (74), there is an indicator variables $I_{R1\text{-}A}$ that exhibit specific effects of some substituents in series of **20**. The indicator variable $I_{R1\text{-}A}$ stands, with a value of unity, for an R^1–substituent that has an aromatic moiety. The positive coefficient of $I_{R1\text{-}A}$ in Eq. (74) suggests that for MMP-1 inhibition the presence of an aromatic group at R^1 position would be beneficial to the activity.

The Eq. 75 for TACE shows linear negative dependence of activity on the ClogP of the compounds. This shows that the activity increase with the decrease in the hydrophobicity of the compounds. The indicator variable $I_{R2\text{-}CC}$ which stands with a value of unity, for an R^2–substituent that is derived from acetylene. The presence of positive coefficient of it suggests that an acetylene-derived R^2-moiety may have a beneficial effect on the TACE inhibition. However, no other indicator variables have been shown to affect the TACE inhibition.

The Eqs. (76) and (77) for MMP-9 and MMP-13 once again exhibit a parallel correlations suggesting the involvement of similar inhibition mechanism for these two enzymes by this series of compounds. These Eqs. (76) and (77) suggest that the increase in inhibition activity of the compounds with the increase in the value of S_N, the E-state index of the nitrogen atom attached to sulfonyl group. The E-state index of an atom is the measure of the availability of π electrons and/or lone pair of electrons on the atom. Thus, the nitrogen atom can be assumed to be involved in some charge-transfer interaction with the enzymes. This is in very good agreement with our previous QSAR studies on MMPs [5-7,22]. However, as in the case for MMP-9 and MMP-13, acetylene-derived R^2-substituents are shown to be detrimental to the activity as indicated by the negative coefficient of the indicator variable $I_{R2\text{-}CC}$. Another indicator variable, I_{AC}, that stands, with a value of unity, for an R^1–substituent containing an aliphatic ring, indicates with its negative coefficient that such an R^1–substituent will also not be conducive to the activity of the compounds against MMP-9 and MMP-13.

For the compounds of Table 3.52, the following correlations were obtained.

MMP-1

$$\log (1/IC_{50}) = 0.444(\pm 0.108)I_{R1\text{-}A} - 2.740(\pm 0.968)\text{ClogP} + 0.672(\pm 0.235)(\text{ClogP})^2 + 8.734(\pm 0.950)$$

$$n = 12,\ r = 0.981,\ r^2_{cv} = 0.91,\ s = 0.06,\ F_{3,8} = 69.69(7.59),\ \text{ClogP}_o = 2.04 \qquad (78)$$

TACE

$$\log (1/IC_{50}) = 0.082(\pm 0.056)S_N - 0.470(\pm 0.280)I_{R1\text{-}A} - 0.965(\pm 0.290)I_{R2\text{-}H} + 9.369\ (\pm 1.191)$$

$$n = 15,\ r = 0.914,\ r^2_{cv} = 0.71,\ s = 0.19,\ F_{3,11} = 18.60(6.22) \qquad (79)$$

In Eq. 78, there exits a parabolic relation between ClogP and inhibition activities of MMP-1 similar to series **20**. The $ClogP_o$ values for MMP-1 is 2.04 beyond which increase in the hydrophobicity increase the inhibition potency of the compounds. The indicator variable $I_{R1\text{-}A}$ in Eqs. (78) and (79) has the same meaning as in Eq. (74), its positive coefficient in Eq. (78) suggests that, as in the series of **20**, the presence of an R^1-substituent with an aromatic moiety will be also beneficial to the inhibition potency of series **21** for MMP-1. The Eqs. 74 and 78 are exactly parallel to each other suggesting the similar way of inhibition of MMP-1 by both the series of compounds. In Eq. 79 for TACE, the activity is majorly governed by electronic term S_N indicating the possibility of charge-transfer interaction and some indicator variables, $I_{R1\text{-}A}$ and $I_{R2\text{-}H}$. $I_{R2\text{-}H}$ stands, with a value of unity, for an R^2–substituent other than H and has a value of zero for H. The negative coefficient of $I_{R1\text{-}A}$ suggests that the presence of an R^1-substituent with an aromatic moiety will be detrimental to the TACE inhibition potency. The negative coefficient of $I_{R2\text{-}H}$ in Eq. (79) suggests that any substituent other than hydrogen at R^2-position will not be conducive to TACE inhibition. It shows that the bulky substituents at both R^1 and R^2 position may create some steric hinderance in TACE inhibition.

All the above Eqs. 19 to 79 exhibit very significant correlations and have very good predictive value as judged from their r^2_{cv}. However, in deriving these equations, some compounds as indicated in their activity tables were not included since they exhibited aberrant behaviors. Since in different equations different compounds were excluded, it was hard to explain in each case the aberrant behaviour of each compound. In such situations, the only reason that can be assigned is the experimental error, or the conformational behavior of the enzymes.

3.10 CONCLUSIONS

The following conclusions have been drawn from the QSAR studies:

1. In the series of sulfonylated amino acids and their corresponding hydroxamate derivatives, the inhibition potency of the compounds against ChC is majorly governed by the electrotopological state (E-state) indices of nitrogen and sulfur atoms. This shows that the nitrogen and sulfur are indicated to play a dominant role in the binding and might be seeking some electronic sites in the enzyme to interact.

2. In functionalized 4-aminoproline hydroxamate derivatives, acyclic amide group present at the 4-position of the 5-membered ring has a positive effect in the inhibition of the MMPs (MMP- 2, 7 and 13). But the presence of cyclic amide group at the same position produces adverse effects (MMP-2, 3, 7 and 13). The R-substitutents of the phenyl ring mostly have advantageous effects. In most of the cases there is a possibility of involvement of sulfonyl group (SO_2) through it sulfur atom or both oxygen atoms in some electronic interactions with the enzymes.

3. In anthranilic hydroxamic acid-based MMP inhibitors the hydrophobic character of the molecules is not beneficial to the activity and in almost all the cases it has the adverse effect. QSAR study points out that the interaction of sulfonamide group with the enzyme can be greatly helped by the presence of the substituents of high electronic characteristics at the sulfonamide nitrogen or at the aromatic rings, affecting the electronic properties of nitrogen or sulfur or of both of sulfonamide group. The large substituents at the aromatic rings however might sometimes produce some steric problems, but those having some electronic character and being of reasonable size might have some electronic interactions with the receptors.

4. In bicyclic heteroaryl hydroxamic acid analogs too the hydrophobic character of the molecules is not advantageous to the activity and in almost all the cases it has the adverse effect, while the polarizability of the molecules seems to favor the inhibition of MMPs. The MMP-9 and MMP-13 behave similarly to these enzymes suggesting that the mechanism of inhibition of these enzymes would be same.

5. In pyranyl hydroxamic acid analogs hydrophobic property of the substituent plays a major role in the inhibition of MMPs. In case of aminosulfonylpyranyl hydroxamic analogs, hydrophobic property of substituents at 3- or 4- position of R^1- moiety which is phenyl or substituted phenyl favors the inhibition potency against MMP-1 and hydrophobic substituents at 2- position of R^1- moiety show detrimental effect against MMP-13 inhibition. In the case of sulfonylpyranyl hydroxamic acid analogs, hydrophobic property of substituents at 2- position of R^2 moiety play a crucial role in the inhibition of MMP-1 and substituents at 4- position of R^2 moiety control the MMP-13 inhibition. Aggrecanase inhibition involves only electronic interaction.

6. In piperidine hydroxamic acid analogs the inhibition of MMPs (MMP-2 and 13) is majorly governed by hydrophobic property of the molecules and the mechanism of inhibition of these two enzymes would be similar.

7. In case of acyclic hydroxamic acid analogs, the results suggest that in few cases the hydrophobic property of the molecules is the major governing factor. However, in some cases, the polarizability of the molecules is shown to be dominant. The two enzymes, MMP-9 and MMP-13, are shown to behave in a similar fashion with any group of inhibitors.

8. In case of piperazine, piperidine and diazepine hydroxamic acid analogs, the results suggest that in most of the cases the hydrophobic property of the molecules plays a major role in the inhibition of the enzymes MMP-1, MMP-9,

MMP-13 and TACE. In many cases, MMP-9 and MMP-13 are shown to behave in a similar fashion with the different group of inhibitors.

9. In the series of benzodiazepine based hydroxamic acid analogs electronic nature of nitrogen atom attached to sulfonyl group and hydrophobic property of the molecule play a major role in the inhibition of MMPs.

10. There exists a typical parabolic (inverted) correlation of hydrophobic property with inhibition potency of MMP-1 in several cases with different series of inhibitors. This change in mechanism can be attributed due to conformational change in the enzyme thereby suggesting that the mechanism of inhibition of MMP-1 would be allosteric.

3.11 FUTURE SCOPE OF WORK

As more and more information about the target is going to be available in future, there is greater scope to carry out higher dimensional drug design strategies over these targets that can be exploited to develop more specific and selective inhibitors of MMPs.

References

[1] Scozzafava, A. and Supuran, C. T. *Protease inhibitors: Synthesis of Clostridium histolyticum collagenase inhibitors incorporating sulfonyl-l-alanine hydroxamate moieties, Bioorg. Med. Chem. Lett. 10*, 499-502 (2000).

[2] Supuran, C. T. and Scozzafava, C. T. *Protease inhibitors – Part 5. Alkyl/arylsulfonyl- and arylsulfonylureido-/arylureido- glycine hydroxamate inhibitors of Clostridium histolyticum collagenases, Eur. J. Pharm. Sci., 10*, 67-76 (2000).

[3] Scozzafava, A. and Supuran, C. T. *Protease inhibitors. Part 8: Synthesis of potent Clostridium histolyticum collagenase inhibitors incorporating sulfonylated l-alanine hydroxamate moieties, Bioorg. Med. Chem., 8*, 637-645 (2000).

[4] Scozzafava, A. and Supuran, C. T. *Protease inhibitors. Part 7 inhibition of Clostridium histolyticum collagenase with sulfonylated derivatives of L-valine hydroxamate, Eur. J. Med. Chem., 35*, 299-307 (2000).

[5] Gupta, S. P., Maheswaran, V., Pande, V. and Kumar, D. *A comparative qsar study on carbonic anhydrase and matrix metalloproteinase inhibition by sulfonylated aminoacid hydroxamates, J. Enzyme Inhib. Med. Chem., 18*, 7-13 (2003).

[6] Kumar, D. and Gupta, S. P. *A quantitative structure–activity relationship study on some matrix metalloproteinase and collagenase inhibitors, Bioorg. Med. Chem., 11*, 421-426 (2003).

[7] Gupta, S. P., Kumar, D. and Kumaran, S. *A quantitative structure–activity relationship study of hydroxamate matrix metalloproteinase inhibitors derived from functionalized 4-aminoprolines, Bioorg. Med. Chem., 11*, 1975-1981 (2003).

[8] Van Wart, H. E. *In Handbook of Proteolytic Enzymes*, Barret, A. J., Rawlings, N. D., Woessner, J. F., Eds., Academic Press, Oxford, pp 368-71 (1998).

[9] Bond, M. D. and Van Wart, H. E. *Purification and separation of individual collagenases of Clostridium histolyticum using red dye ligand chromatography, Biochemistry, 23*, 3077-3085 (1984).

[10] Bond, M. D. and Van Wart, H. E. *Characterization of the individual collagenases from Clostridium histolyticum, Biochemistry, 23*, 3085-3091 (1984).

[11] Van Wart, H. E. and Stienbrink, D. R. *A continuous spectrophotometric assay for Clostridium histolyticum collagenases, Anal. Biochem., 113*, 356-365 (**1981**).

[12] Matsushita, O., Jung, C. M., Minami, J., Katayama, S., Nishi, N. and Okabe, A. *A study of the collagen-binding domain of a 116-kDa Clostridium histolyticum collagenases, J. Biol. Chem., 273*, 3643-3648 (**1998**).

[13] Jung, C. M., Matsushita, O., Katayama, S., Minami, J., Sakurai, J. and Okabe, A. J. *Identification of metal ligands in the Clostridium histolyticum collagenases, J. Bacteriol., 181*, 2816-2822 (**1999**).

[14] Grobelny, D. and Galardy, R. E. *Aldehyde and ketone substrate analogues inhibit the collagenase of Clostridium histolyticum, Biochemistry, 24*, 6145-6152 (**1985**).

[15] Jeng, A. Y., Chou, M. and Parker, D. T. *Sulfonamide-based hydroxamic acids as potent inhibitors of mouse macrophage metalloelastase, Bioorg. Med. Chem. Lett., 8*, 897-902 (**1998**).

[16] Hanessian, S., Bouzbouz, S., Boudon, A., Tucker, G. C. and Peyroulan, D. *Picking the S1, S1' and S2' pockets of matrix metalloproteinases: A niche for potent acyclic sulfonamide inhibitors, Bioorg. Med. Chem. Lett., 9*, 1691-1696 (**1999**).

[17] Natchus, M.G., Bookland, R.G., De, B., Almstead, N.G., Pikul, S., Janusz, M.J., Heitmeyer, S.A., Hookfin, E.B., Hsieh, L.C., Dowty, M.E., Dietsch, C.R., Patel, V.S., Garver, S.M., Gu, F., Pokross, M.E., Mieling, G.E., Baker, T.R., Foltz, D.J., Peng, S.X., Bornes, D.M., Strojnowski, M.J. and Taiwo, Y.O. *Development of new hydroxamate matrix metalloproteinase inhibitors derived from functionalized 4-aminoprolines, J. Med. Chem., 43*, 4948-4963 (**2000**).

[18] Levin, J. I., Du, M. T., DiJoseph, J. F., Killar, L. M., Sung, A., Walter, T., Sharr, M. A., Roth, C. E., Moy, F. J., Powers, R., Jin, G., Cowling, R. and Skotnicki, J. S. *The Discovery of anthranilic acid-based MMP inhibitors. Part 1: SAR of the 3-position, Bioorg. Med. Chem. Lett., 11*, 235-238 (**2001**).

[19] Levin, J. I., Chen, J., Du, M., Hogan, M., Kincaid, S., Nelson, F. C., Venkatesan, A. M., Wehr, T., Zask, A., DiJoseph, J., Killar, L. M., Skala, S., Sung, A., Sharr, M., Roth, C., Jin, G., Cowling, R., Mohler, K. M., Black, R. A., March, C. J. and Skotnicki, J. S. *The discovery of anthranilic acid-based MMP inhibitors. Part 2: SAR of the 5-position and P1' groups, Bioorg. Med. Chem. Lett., 11*, 2189-

2192 (**2001**).

[20] Levin, J. I., Chen, J. M., Du, M. T., Nelson, F. C., Wher, T., DiJoseph, J. F., Killar, L. M., Skala, S., Sung, A., Sharr, M. A., Roth, C. E., Jin, G., Cowling, R., Di, L., Sherman, M., Xu, Z. B., March, C. J., Mohler, K. M., Black, R. A, and Skotnicki, J. S. *The discovery of anthranilic acid-based MMP inhibitors. Part 3: Incorporation of basic amines*, *Bioorg. Med. Chem. Lett.*, *11*, 2975-2978 (**2001**).

[21] Levin, J. I., Chen, J. M., Du, M. T., Nelson, F. C., Killar, L. M., Skala, S., Sung, A., Jin, G., Cowling, R., Barone, D., March, C. J., Mohler, K. M., Black, R. A. and Skotnicki, J. S. *Anthranilate sulfonamide hydroxamate TACE inhibitors. Part 2: SAR of the acetylenic P1' group*, *Bioorg. Med. Chem. Lett.*, *12*, 1199-1202 (**2002**).

[22] Gupta, S. P. and Kumaran, S. *A quantitative structure–activity relationship study on Clostridium histolyticum collagenase inhibitors: Roles of electrotopological state indices*, *Bioorg. Med. Chem.*, *11*, 3065-3071 (**2003**).

[23] Zask, A., Gu, Y., Albright, J. D., Du, X., Hogan, M., Levin, J. I., Chen, J. M., Killar, L. M., Sung, A., DiJoseph, J. F., Sharr, M. A., Roth, C. E., Skala, S., Jin, G., Cowling, R., Mohler, K. M., Barone, D., Black, R., March, C. and Skotnicki, J. S. *Synthesis and SAR of bicyclic heteroaryl hydroxamic acid MMP and TACE inhibitors*, *Bioorg. Med. Chem. Lett.*, *13*, 1487-1490 (**2003**).

[24] Reiter, L. A., Robinson, R. P., McClure, K. F., Jones, C. S., Reese, M. R., Mitchell, P. G., Otterness, I. G., Bliven, M. L., Liras, J., Cortina, S. R., Donahue, K. M., Eskra, J. D., Griffiths, R. J., Lame, M. E., Lopez-Anaya, A., Martinelli, G. J., McGahee, S. M., Yocum, S. A.,Lopresti-Morrow, L. L., Tobiassen, L. M. and Vaughn-Bowser, M. L. *Pyran-containing sulfonamide hydroxamic acids: Potent MMP inhibitors that spare MMP-1*, *Bioorg. Med. Chem. Lett.*, *14*, 3389-3395 (**2004**).

[25] Noe, M. C., Snow, S. L., Wolf-Gouveia, L. A., Mitchell, P. G., Lopresti-Morrow, L., Reeves, L. M., Yocum, S. A., Liras, J. L. and Vaughn, M. *3-Hydroxy-4-arylsulfonyltetrahydropyranyl-3-hydroxamic acids are novel inhibitors of MMP-13 and aggrecanase*, *Bioorg. Med. Chem. Lett.*, *14*, 4727-4730 (**2004**).

[26] Barta, T. E., Becker, D. P., Bedell, L. J., De Crescenzo, G. A., McDonald, J. J., Mehta, P., Munie, G. E. and Villamil, C. I. *Selective, orally active MMP inhibitors*

with an aryl backbone, Bioorg. Med. Chem. Lett., *11*, 2481 (**2000**).

[27] Barta, T. E., Becker, D. P., Bedell, L. J., De Crescenzo, G. A., McDonald, J. J., Munie, G. E., Rao, S., Shieh, H.-S., Stegeman, R., Stevens, A. M. and Villamil, C. I. *Synthesis and activity of selective MMP inhibitors with an aryl backbone, Bioorg. Med. Chem. Lett., 10*, 2815 (**2000**).

[28] Martin, F. M., Beckett, P. R., Bellamy, C. L., Courtney, P. F., Davies, S. J., Drummond, A. H., Dodd, R., Pratt, L. M., Patel, S. R., Ricketts, M. L., Todd, R. S., Tuffnell, A. R., Ward, J. W. S. and Whittaker, M. *The synthesis and biological evaluation of non-peptidic matrix metalloproteinase inhibitors, Bioorg. Med. Chem. Lett., 9*, 2887 (**1999**).

[29] Levin, J. I., Chen, J. M., Cheung, K., Cole, D., Crago, C., Santos, E. D., Du, X., Khazova, G., MacEwan, G., Niu, C., Salaski, E. J., Zask, A., Cummons, T., Sung, A., Xu, J., Zhang, Y., Xu, W., Ayral-Kaloustian, S., Jin, G., Cowling, R., Barone, D., Mohler, K. M., Black, R. A. and Skotnicki, J. S. *Acetylenic TACE inhibitors. Part 1. SAR of the acyclic sulfonamide hydroxamates, Bioorg. Med. Chem. Lett., 13*, 2799-2803 (**2003**).

[30] Becker, D. P., Barta, T. E., Bedell, L., DeCrescenzo, G., Freskos, J., Getman, D. P., Hockerman, S. L., Li, M., Mehta, P., Mischke, B., Munie, G. E., Swearingen, C. and Villamila, C. I. *α-amino-β-sulphone hydroxamates as potent MMP-13 inhibitors that spare MMP-1, Bioorg. Med. Chem. Lett., 11*, 2719-2722 (**2001**).

[31] Venkatesan, A. M., Grosu, G. T., Davis, J. M., Baihua, H., Ellingboe, J., Baker, J. L., Skotnicki, J. S., Arie, Z., DiJoseph, J. F., Sung, A., Michele, A. S., Killar, L. M., Thomas, W., Guixian, J. and Cowling, R. *Synthesis and structure-activity relationship of α-sulfonylhydroxamic acids as novel, orally active matrix metalloproteinase inhibitors for the treatment of osteoarthritis, J. Med. Chem., 46*, 2361-2375 (**2003**).

[32] Letavic, M. A., Barberia, J. T., Carty, T. J., Hardink, J. R., Liras, J., Lopresti-Morrow, L. L., Mitchell, P. G., Noe, M. C., Reeves, L. M., Snow, S. L., Stam, E. J., Sweeney, F. J., Vaughn, M. L. and Yu, C. H. *Synthesis and biological activity of piperazine-based dual MMP-13 and TNF-alpha converting enzyme inhibitors, Bioorg. Med. Chem. Lett., 13*, 3243-3246 (**2003**).

[33] Letavic, M. A., Axt, M. Z., Barberia, J. T., Carty, T. J., Danley, D. E., Geoghegan, K. F., Halim, N. S., Hoth, L. R., Kamath, A. V., Laird, E. R., Lopresti-Morrow, L. L., McClure, K. F., Mitchell, P. G., Natarajan, V., Noe, M. C., Pandit, J., Reeves, L., Schulte, G. K., Snow, S. L., Sweeney, F. J., Tan, D. H. and Yu, C. H. *Synthesis and biological activity of selective pipecolic acid-based TNF-alpha converting enzyme (TACE) inhibitors, Bioorg. Med. Chem. Lett., 12,* 1387-1390 **(2002)**.

[34] Venkatesan, A. M., Davis, J. M., Grosu, G. T., Baker, J. L., Ellingboe, J., Arie, Z., Levin, J. I., Sandanayaka, V. P., Milla, D., Skotnicki, J. S., DiJoseph, J. F., Sung, A., Michele, A. S., Killar, L. M., Thomas, W., Guixian, J., Cowling, R., Tillett, J., Weiguang, Z., McDevitt, J. and Zhang, B. X. *Synthesis and structure-activity relationship of N-substituted 4-arylsulfonylpiperidine-4-hydroxamic acids as novel, orally active matrix metalloproteinase inhibitors for the treatment of osteoarthritis, J. Med. Chem., 46,* 2376-2396 **(2003)**.

[35] Levin, J. I., DiJoseph, J. F., Killar, L. M., Sung, A., Walter, T., Sharr, M. A., Roth, C. A., Skotnicki, J. S. and Albright, J. D. *The synthesis and biological activity of a novel series of diazepine MMP inhibitors, Bioorg. Med. Chem. Lett., 8,* 2657-2662 **(1998)**.

[36] Nelson, F.C., Santos, E.D., Levin. J.I., Chen, J.M., Skotnicki, J.S., DiJoseph, J.F., Sharr, M.A., Sung, A., Killar, L.M., Cowling, R., Jin, G., Roth, C.E. and Albright, J.D. *Benzodiazepine inhibitors of the MMPs and TACE, Bioorg. Med. Chem. Lett. 12,* 2867-2870 **(2002)**.

[37] Levin, J.I., Nelson, F.C., Santos, E.D., Du, M.T., MacEwan, G., Chen, J.M., Ayral-Kaloustian, S., Xu, J., Jin, G., Cummons, T. and Barone, D. *Benzodiazepine inhibitors of the MMPs and TACE. Part 2, Bioorg. Med. Chem. Lett., 14,* 4147-4151 **(2004)**.

List of Publications

1. Gupta, S. P., Kumar, D. and Kumaran, S. *A quantitative structure–activity relationship study of hydroxamate matrix metalloproteinase inhibitors derived from functionalized 4-aminoprolines, Bioorg. Med. Chem., 11*, 1975-1981 (**2003**).
2. Gupta, S. P. and Kumaran, S. *A quantitative structure–activity relationship study on Clostridium histolyticum collagenase inhibitors: Roles of electrotopological state indices, Bioorg. Med. Chem., 11*, 3065-3071 (**2003**).
3. Gupta, S. P. and Kumaran, S. *Quantitative structure-activity relationship studies on some series of anthranilic acid-based matrix metalloproteinase inhibitors, Bioorg. Med. Chem., 13*, 5454-5462 (**2005**).
4. Gupta, S. P. and Kumaran, S. *Quantitative structure-activity relationship studies on matrix metalloproteinase inhibitors: Bicyclic heteroaryl hydroxamic acid analogs, Lett. Drug Des. Discov.*, In press.
5. Gupta, S. P. and Kumaran, S. *Quantitative structure-activity relationship studies on matrix metalloproteinase inhibitors: Piperazine, Piperidine and Diazepine hydroxamic acid analogs, QSAR & Comb. Sci.*, Accepted.

Communicated

6. Gupta, S. P. and Kumaran, S. *Quantitative structure-activity relationship studies on matrix metalloproteinase inhibitors: Piperidine sulfonamide aryl hydroxamic acid analogs, Bioorg. Med. Chem. Lett.*, Communicated.
7. Gupta, S. P., Kumaran, S. and Bagaria, P. *Quantitative structure-activity relationship studies on matrix metalloproteinase inhibitors: Pyranyl hydroxamic acid analogs, J. Enzyme Inhib. Med. Chem.*, Communicated.
8. Gupta, S. P. and Kumaran, S. *Quantitative structure-activity relationship studies on matrix metalloproteinase inhibitors: Acyclic hydroxamic acid analogs, Bioorg. Med. Chem.*, Communicated.

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1. *Current Medicinal Chemistry-Cardiovascular and Hematological Agents*
2. *Current Computer-Aided Drug Design*
3. *Current Enzyme Inhibition*
4. *Current Bioinformatics*

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