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Review

Matrix metalloproteinases (MMPs): Chemical–biological functions and (Q)SARs

Rajeshwar P. Verma* and Corwin Hansch

Department of Chemistry, Pomona College, 645 North College Avenue, Claremont, CA 91711, USA

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Abstract—Matrix metalloproteinases (MMPs) are a large family of calcium-dependent zinc-containing endopeptidases, which are responsible for the tissue remodeling and degradation of the extracellular matrix (ECM), including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan. They are regulated by hormones, growth factors, and cytokines, and are involved in ovarian functions. MMPs are excreted by a variety of connective tissue and pro-inflammatory cells including fibroblasts, osteoblasts, endothelial cells, macrophages, neutrophils, and lymphocytes. These enzymes are expressed as zymogens, which are subsequently processed by other proteolytic enzymes (such as serine proteases, furin, plasmin, and others) to generate the active forms. Matrix metalloproteinases are considered as promising targets for the treatment of cancer due to their strong involvement in malignant pathologies. Clinical/preclinical studies on MMP inhibition in tumor models brought positive results raising the idea that the development of strategies to inhibit MMPs may be proved to be a powerful tool to fight against cancer. However, the presence of an inherent flexibility in the MMP active-site limits dramatically the accurate modeling of MMP–inhibitor complexes. The interest in the application of quantitative structure–activity relationships (QSARs) has steadily increased in recent decades and we hope it may be useful in elucidating the mechanisms of chemical–biological interactions for this enzyme. In the present review, an attempt has been made to explore the in-depth knowledge from the classification of this enzyme to the clinical trials of their inhibitors. A total number of 92 QSAR models (44 published and 48 new formulated QSAR models) have also been presented to understand the chemical–biological interactions. QSAR results on the inhibition of various compound series against MMP-1, -2, -3, -7, -8, -9, -12, -13, and -14 reveal a number of interesting points. The most important of these are hydrophobicity and molar refractivity, which are the most important determinants of the activity.

Contents

Keywords: MMPs; Apoptosis; Chemical–biological interactions; Hydrophobicity; Molar refractivity; QSARs.
* Corresponding author. Tel.: +1 909 607 4249; fax: +1 909 607 7726; e-mail: rverma@pomona.edu

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1. Introduction

Matrix metalloproteinases (MMPs) are a large family of calcium-dependent zinc-containing endopeptidases, which are responsible for the tissue remodeling and degradation of the extracellular matrix (ECM), including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan. MMPs are usually minimally expressed in normal physiological conditions and thus homeostasis is maintained. However, MMPs are regulated by hormones, growth factors, and cytokines, and are involved in ovarian functions. Endogenous MMP inhibitors (MMPIs) and tissue inhibitors of MMPs (TIMPs) strictly control these enzymes. Over-expression of MMPs results in an imbalance between the activity of MMPs and TIMPs that can lead to a variety of pathological disorders.[1–5] A list of physiological and pathological processes for which MMPs have been implicated is shown in Table 1.[5,6] The earliest descriptions of MMPs were in 1949 as depolymerizing enzymes which, it was proposed, could facilitate tumor growth by making connective tissue stroma, including that of small blood vessels, more fluid. About after 13 years, the first vertebrate MMP, collagenase, was isolated and characterized as the enzyme responsible for the resorption by tadpole tail. During the next 20 years, several mammalian enzymes were partially purified, but it was not until 1985 that the field really developed when structural homologies became apparent, allowing many new members to be identified through the techniques of molecular biology.[7] In a recent work, it was concluded that smoking alters the levels of matrix metalloproteinases in skin tissue, serum, and saliva, which may affect the turnover of extracellular matrix (ECM) of skin.[8]

Table 1. Involvement of MMPs in physiological and pathological processes

Physiological processes	Pathological processes	
Angiogenesis	Arthritis	Multiple sclerosis
Apoptosis	Alzheimer's disease	Nephritis
Blastocyst implantation	Atherosclerosis	Neurological disease
Bone remodeling	Breakdown of blood–brain barrier	Osteoarthritis (OA)
Cervical dilation	Cancer	Periodontal disease
Embryonic development	Cardiovascular disease	Rheumatoid
Endometrial cycling	Central nervous system disorders	Skin ulceration
Hair follicle cycling	Corneal ulceration	Sorby's fundus disease
Immune response	Emphysema	Vascular disease
Inflammation	Fibrotic lung disease	
Nerve growth	Gastric ulcer	
Organ morphogenesis	Guillian-Barre disease	
Ovulation	Liver cirrhosis	
Postpartum uterine involution	Liver fibrosis	
Wound healing	Metastasis	

Matrix metalloproteinases are excreted by a variety of connective tissue and pro-inflammatory cells including fibroblasts, osteoblasts, endothelial cells, macrophages, neutrophils, and lymphocytes. These enzymes are expressed as zymogens, which are subsequently processed by other proteolytic enzymes (such as serine proteases, furin, plasmin, and others) to generate the active forms. Under normal physiological conditions, the proteolytic activity of the MMPs is controlled at any of the following three known stages: activation of the zymogens, transcription, and inhibition of the active forms by various tissue inhibitors of MMPs (TIMPs). In pathological conditions this equilibrium is shifted toward increased MMP activity leading to tissue degradation.[9,10]

MMPs have now been considered as a promising target for cancer therapy and a large number of synthetic and natural MMP inhibitors (MMPIs) have been identified as cytostatic and anti-angiogenic agents, and have begun to undergo clinical trials in view of their specific implication in malignant tissues. Although preclinical studies were compelling to encourage several clinical trials, the past years have seen a consistent number of disappointing results and/or limited success. The critical examination of previous results has prompted serious re-evaluation of MMP-inhibition strategies focusing the attention of future research on the identification of specific MMP targets in tumors at different stages of tumor progression, both in order to improve efficacy and to reduce the side-effect profile.[11,12]

A search from SciFinder Scholar (2006 Edition) of the Chemical Abstract reveals that there are over 26,400

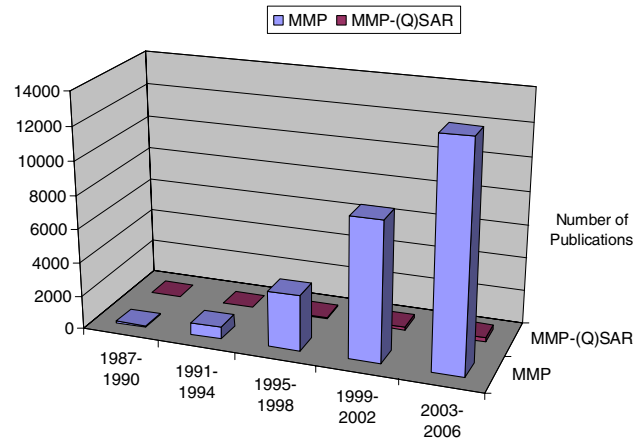

Figure 1. Histogram of publications on MMPs and MMPs-(Q)SAR during the years of 1987 and 2006 (from January 1987 to July 2006).

publications (journal articles, patents, and abstracts) on MMPs made during the years of 1987 and 2006 (from January 1987 to July 2006), which includes about 550 publications on MMPs-(Q)SAR [(quantitative) structure–activity relationships]. A histogram of publications on MMPs and MMPs-(Q)SAR during the years of 1987 and 2006 reflects fluctuation of interest and research intensity (Fig. 1).

2. Classification

To date at least 26 human MMPs are known (see Table 2). On the basis of their specificity, these MMPs are classified into collagenases, gelatinases, stromelysins, and matrilysins. Another subclass of MMPs is represented by the membrane-type MMPs (MT-MMPs) that additionally contain a transmembrane and intracellular domain, a membrane linker domain, or are membrane associated.[7,13,14] A histogram for the publication of 26 MMPs during 1987–2005 is shown in Figure 2.

3. Structural studies

Most of the matrix metalloproteinases consist of four distinct domains, which are N-terminal pro-domain, catalytic domain, hinge region, and C-terminal hemopexin-like domain. This may be responsible for the macromolecular substrate recognition as well as for interaction with TIMPs. The membrane-type MMPs (MT-MMPs) contain an additional transmembrane domain that anchors them in the cell surface.[15] The advent of high-resolution X-ray and NMR structures has provided new paradigms for the design of MMP inhibitors in general and selective inhibitors in particular.[16] X-ray and/or NMR structures are publicly available for nine out of 26 known human MMPs. Reliable structures of the catalytic domains of the remaining MMPs were obtained by comparative modeling utilizing a significant sequence identity in these areas (56–64%). The rich structural information makes MMPs an exemplary case for development of selective inhibitors using computational tools.[17]

Table 2. Classification of matrix metalloproteinase enzymes

No.	MMP No.	Class	Enzyme
1	MMP-1	Collagenases	Collagenase-1
2	MMP-8		Neutrophil collagenase
3	MMP-13		Collagenase-3
4	MMP-18		Collagenase-4
5	MMP-2	Gelatinases	Gelatinase-A
6	MMP-9		Gelatinases-B
7	MMP-3	Stromelysins	Stromelysin-1
8	MMP-10		Stromelysin-2
9	MMP-11		Stromelysin-3
10	MMP-27		Homology to stromelysin-2 (51.6%)
11	MMP-7	Matrilysins	Matrilysin (PUMP)
12	MMP-26		Matrilysin-2
13	MMP-14	MT-MMP (membrane type)	MT1-MMP
14	MMP-15		MT2-MMP
15	MMP-16		MT3-MMP
16	MMP-17		MT4-MMP
17	MMP-24		MT5-MMP
18	MMP-25		MT6-MMP
19	MMP-12	Other enzymes	Macrophage metalloelastase
20	MMP-19		RASI 1
21	MMP-20		Enamelysin
22	MMP-21		MMP identified on chromosome 1
23	MMP-22		MMP identified on chromosome 1
24	MMP-23		From human ovary cDNA
25	MMP-28		Epilysin
26	MMP-29		Unnamed

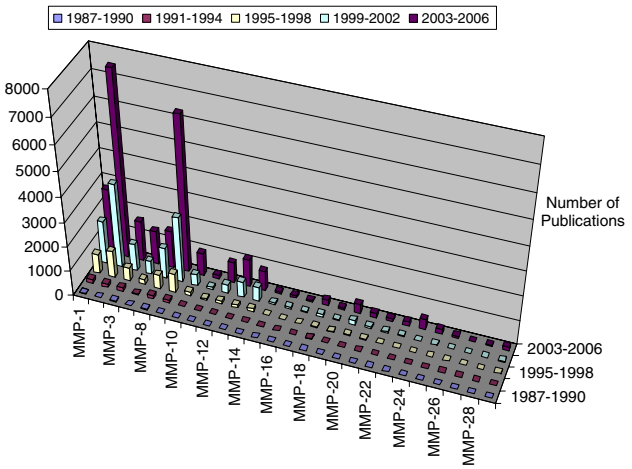

Figure 2. Histogram of publications on various MMPs during the years of 1987 and 2006 (from January 1987 to July 2006).

The first structure of an MMP in complex with a synthetic inhibitor (MMP-1 catalytic domain) was reported about 11 years ago by Lovejoy and co-workers.[18] This structure reveals that the active site of MMP is a shallow cleft with a flat unprimed side and a narrow primed side centered around the S1′ pocket. Since this first report, many other MMP–inhibitor complexes have been solved and found that the MMP catalytic domains share a marked sequence similarity, where the percentage of identical residues ranges from a minimum of 33% between MMP-21 and MMP-23, to a maximum of

86% between MMP-3 and MMP-10.[19] A comparison of such sequence similarity with the available 3D structure shows that the overall topology of the enzyme active-site is highly conserved between the different MMPs, with the two significant emerging features that are the depth of S1′ pocket and the length as well as composition of the loop constituting the outside wall of the S1′ pocket.[20] A recent report describes the structure of MMP-2 in which the catalytic domain possess a similar overall topology characterized by a twisted five-stranded β-sheet, containing four parallel strands and one antiparallel strand, and three long α-helices.[21]

It has also been observed that the conserved active-site sequence motif HEXXHXXGXXH coordinates the catalytic zinc(II) ion and contains the glutamic acid residue which facilitates catalysis. The substrate binding groove, which is relatively open at S3–S1 and S3′, narrow at S1′ and S2′ with the S1′ site being a well-defined pocket, penetrates the surface of the enzyme. The presence of second 'structural' zinc(II) ion and two or three calcium(II) ions has been confirmed. Thus, it has been difficult to obtain recombinant full-length enzymes suitable for structural determination. MMP-7, one of the smallest members of the MMP family, does not possess a C-terminal domain, whose inhibitor complexes possess broadly similar structures to that of the catalytic domains of MMP-1, MMP-3, and MMP-8.[7] This C-terminal domain is found to be present in almost all of the MMPs except MMP-7 and MMP-23, and seems to regulate the enzyme activity.[22]

A significant interaction between MMPs and their substrates/or inhibitors has been demonstrated between S1′ subsite and the P1′ residue. There is a variation between MMPs in the amino acid residues, which form the S1′ pocket.[7] It has been shown that the modifications of the P1′ portion of the molecule play a key role affecting both the potency and selectivity within the MMP family. Longer-chain aliphatic substituents in this region of the molecule tend to increase potency for MMP-3 and decrease potency for MMP-1, while aromatic substituents seem to generate broad-spectrum inhibition.[23]

From the X-ray crystallography and homology modeling MMPs may be classified into two broad structural classes depending on the depth of the S1′ pocket. This selective pocket is relatively deep for most MMP enzymes (e.g., MMP-2, MMP-3, MMP-8, MMP-9, MMP-13, etc.), but for certain MMP enzymes (e.g., MMP-1, MMP-7, and MMP-11) it is partially or completely occluded due to an increase in the size of the side chain of the amino acid at position 193 (MMP-8 numbering) from leucine to arginine (MMP-1), tyrosine (MMP-7), glutamine (MMP-11), or one of the amino acid residues that form the pocket. It has also been shown that the mutation of S1′ subunit tyrosine of MMP-7 to leucine changes the substrate specificity to be more like that of the deep pocket enzyme MMP-3.[24] Homology models for MMP-2 and MMP-9 based on the structure of MMP-3 suggest that there may be differences in the shape of the bottom of the S1′ subunit for the deep pocket enzymes.[25] In the case of MMP-2, the S1′ pocket may be a channel with no bottom, whereas that for MMP-9 is said to be a pocket-like subsite. The subunit (S2′) is a solvent-exposed cleft, with hydrophobic P2′ residues in both substrates and inhibitors. The S3′ subunit is a really ill-defined solvent-exposed region. While there are some variations in residues for this subsite for the various MMPs, the introduction of different P3′ substituents in general tends to have only a modest effect on inhibitory selectivity.[7]

An NMR structural study of MMP-1 catalytic domain suggests that substantial structural changes occur in the active-site cleft on the binding of an inhibitor.[26] Conformational changes have also been observed in the active site between X-ray structures of MMP-3 catalytic domain and different inhibitors bound.[27] Thus, structural information must be considered in the design of MMP inhibitors.

4. Reaction mechanism

The reaction mechanism for the proteolysis by MMPs has been delineated on the basis of structural information[28,29] and shown in Figure 3.[29] It is proposed that the scissile amide carbonyl coordinates to the active-site zinc(II) ion. This carbonyl is attacked by a water molecule, which is both hydrogen bonded to a conserved glutamic acid (Glu-198 in MMP-8) and coordinated to the zinc(II) ion. The water molecule donates a proton to the Glu residue that transfers it to the nitrogen of the scissile amide, which is followed by the Glu residue shuttling the

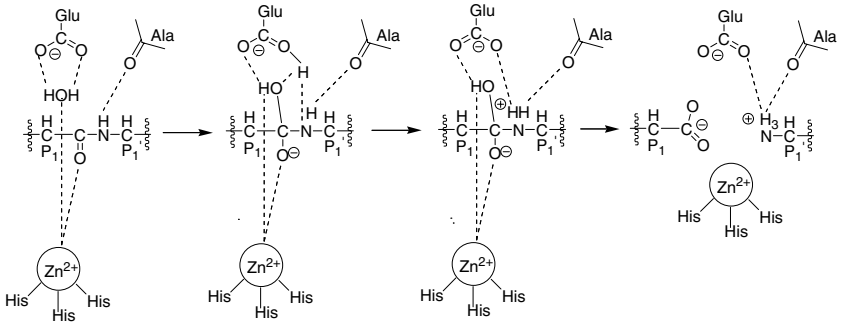

Figure 3. Reaction mechanism for the proteolysis by MMPs. Reprinted with permission from Ref. 29. Copyright 1994 American Chemical Society.

remaining proton from the water molecule to the nitrogen of the scissile amide with resultant peptide bond cleavage. In this process, the positively charged zinc(II) ion helps to stabilize a negative charge at the carbon of the scissile amide and a conserved alanine (Ala-161 in MMP-8) residue helps stabilize positive charge at the nitrogen of the scissile amide.[7,29]

5. Active site

The active site consists of two distinct regions: a groove in the protein surface centered on the catalytic zinc ion and an S1′ specificity site that varies considerably among members of the family. Bound inhibitors adopt extended conformations within the groove, make several β-structure-like hydrogen bonds with the enzyme, and provide the fourth ligand for the catalytic zinc ion. The S1′ subset apparently plays a significant role in determining the substrate specificity in the active enzymes. The volume of this subsite varies widely, with a relatively small hydrophobic site in MMP-7 and MMP-1 as compared with a very large site in MMP-8 and a site that extends all the way through the MMP-3 molecule, open to solution at both ends.[30] In Figure 4, there is a schematic representation of hexapeptide substrate bound into an MMP-8 active-site that shows the binding of Zn^{2+} to His197.[7,31] There is a variation between the MMPs in the amino acid residues that form the S1′ pocket. A selected variable residue in the active site of the MMPs has been shown in Table 3.[7]

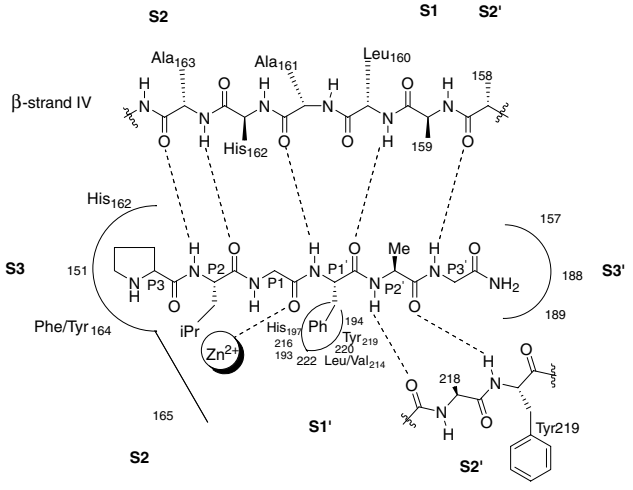

Figure 4. Schematic representation of MMP-8 active-site. Reprinted with permission from Ref. 7. Copyright 1999 American Chemical Society.

6. Substrate selectivity

It has been established that the various MMPs exhibit different selectivities for the various matrix proteins. Thus, it is of interest in understanding such substrate selectivity to identify optimized peptide substrates for assay development as well as to design the selective MMP inhibitors. Some studies have been performed to determine the sequence of the cleavage site in protein substrates for individual enzymes.[32–34] In the majority of cases, the variation of substitution provides a gradation of selectivity and there are very few substitutions that provide significant differential selectivity between the enzymes. The preferred amino acid at P3 is proline for all the kinds of examined enzymes. Arg is preferred at P2 for MMP-2 selectivity, whereas Leu and Met are preferred for MMP-7. Phage-displayed results indicate that Phe is preferred over Leu and Met at P2 for MMP-3.[7,35] Val at P1 results in negligible cleavage for all of the enzymes. At the P1 position, Glu provides significant cleavage by MMP-7 and MMP-8, and negligible by MMP-1, MMP-2, and MMP-9. At P1′, the presence of a Tyr residue results in highly selective cleavage by MMP-8 as well as Leu and Met appear to be preferred for broad-spectrum cleavage; however, on the other hand, the phage-displayed results suggest that Met at P1′ gives minimal cleavage with MMP-7. However, the substrate specificity studies suggest that Phe at P1′ is preferred for cleavage by MMP-3 over the other enzymes, whereas the phage-displayed results indicate that Phe at P1′ provides negligible cleavage.[7] It has also been shown that MMP-11 and MMP-14 cleave substrates containing unusual amino acids with extremely long side chains at their P1′ position more efficiently than the corresponding substrates with natural phenylalanine or leucine amino acids.[7,36] The present studies suggest that there is a very little selectivity by the various

Table 3. Selected variable residues in the active site of MMPs

Residue No.	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-10	MMP-11	MMP-12	MMP-13	MMP-14
151	Ser	Tyr	Tyr	Tyr	Ser	Tyr	Tyr	Leu	His	Tyr	Thr
157	Gly	Asp	Gly	Gly	Asn	Asp	Gly	Gly	Gly	Ser	Gly
158	Gly	Gly	Asn	Asn	Gly	Gly	His	Gly	Gly	Gly	Gly
159	Asn	Leu	Val	Thr	Ile	Leu	Ser	Ile	Ile	Leu	Phe
165	Gln	Ala	Ala	Ala	Gln	Pro	Pro	Phe	Gly	Pro	Phe
188	Glu	Gly	Gly	Gly	Asn	Gly	Gly	Gly	Gly	Gly	Gly
189	Tyr	Tyr	Thr	Ile	Tyr	Tyr	Thr	Thr	Thr	Tyr	Asn
193	Arg	Leu	Leu	Tyr	Leu	Leu	Leu	Gln	Leu	Leu	Leu
194	Val	Val	Val	Ala	Val	Val	Val	Val	Thr	Val	Val
218	Ser	Ile	Leu	Thr	Asn	Met	Leu	Phe	Thr	Ile	Phe
220	Thr	Thr	His	Gly	Ala	Arg	Asn	Thr	Lys	Thr	Gln
222	Ser	The	Leu	Gly	Arg	Thr	Phe	Arg	Val	Thr	Met

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substitutions at P2′ position and that generally Trp is preferred for efficient cleavage. The same is true for amino acid changes at P3′. However, there is a contradiction between substrate and phage studies; the former suggests a strong preference of Met at P3′ for selective cleavage by MMP-7, whereas the latter indicates that Met at P3′ results in poor cleavage by MMP-7.[7,35,37]

The S3–S1 subsites from a shallow region bordered on one side by the β-strand IV that features a hydrophobic proline binding cleft at S3. Proline is a preferred P3 group in MMP substrates and the structure of the left-hand side inhibitor Pro-Leu-Gly-NHOH ligated to the catalytic domain of MMP-8 illustrates the tight complementarity in proline binding at S3. This inhibitor binds anti-parallel to the β-strand IV by two backbone hydrogen bond interactions (via NH of P3–P2 amide and carbonyl of P2–P1 amide) with the P2 leucine residing in a shallow cleft and the carbonyl of the P3–P2 amide and NH of the P2–P1 amide exposed to solvent. Differences between the various MMPs in the S3–S1 region are relatively subtle.[7,31,38] It is interesting to note that the selective replacement of catalytic zinc of MMP-3 catalytic domain with other transition metals that are Co^{2+}, Mn^{2+}, Cd^{2+}, and Ni^{2+} results in the retention of protease activity. However, substitution of the catalytic metal influences the substrate specificity of enzyme, since the active-site geometry is altered and hence affects substrate binding.[39]

At present, the selectivity of the most known MMP inhibitors relies on the two dominant molecular features: (a) chelating moiety that interacts with the catalytic zinc ion and (b) hydrophobic extensions protruding from the catalytic site into the large and hydrophobic S1′ pocket (P1′ group). Since the structural differences between MMP families occur mainly in the S1′ subsite, modifications of the P1′ group have been utilized to introduce inhibitor selectivity.[2]

7. MMPs and apoptosis

Apoptosis, also known as programmed cell death (PCD), is an extremely well-ordered process by which unwanted, defective, or damaged cells are rapidly and selectively eliminated from the body. MMPs play an intriguing role in PCD, showing both apoptotic and anti-apoptotic action (Table 4).[40] MMPs affect cell survival and proliferation both positively and negatively by regulating 'survival signals' generated by specific adhesive events; these particular effects of MMPs may reflect the differences in MMP substrates involved in each response.[40–43] There is an increasing in vitro evidence for the involvement of MMP-9 in the apoptosis phenomena observed in developing cerebellum, as well as in retinal ganglion cells.[44–46] Neuronal apoptosis may be triggered by the MMP-dependent cleavage of stromal cell-derived factor-α, a *Chemokine* converted to a highly neurotoxic protein leading to neurodegeneration after a precise processing by active MMP-2.[47]

Table 4. Paradoxically opposing functions of MMPs in PCD

Pro-apoptotic effects	Anti-apoptotic effects
MMP-1	MMP-2
MMP-2	MMP-3
MMP-3	MMP-7
MMP-7	MMP-9
MMP-9	MMP-11
MMP-11	

MMPs can interact with cell surface receptors and may, in this way, stimulate apoptosis. As for example, MMP-9 may trigger neuronal cell death through the association with lipoprotein receptor-related protein, a cell surface protein that has been linked to changes in the activation status of intracellular signaling molecules following its engagements by tissue-plasminogen activator.[48,49] MMPs may also cleave other cell surface receptors, including proteinase-activated receptors (i.e., MMP-12); in this way, MMPs are involved in shedding of ICAM and CD44 during apoptosis of endothelial and epithelial cells.[41,46] The modulation by MMPs of the cell surface death receptor-mediated neuronal apoptosis suggests that MMP-3 may have an anti-apoptotic effect, playing a key role in neurodegeneration.[50,51]

Recently, it has been observed that the proteolytic activity of MMPs plays opposing roles on PCD (Table 4). In this respect, interesting evidence was demonstrated by MMP-7, which is able to release membrane-bound Fas Ligand (FasL), a transmembrane stimulator of the death receptor Fas (CD95/Apo-1); released FasL induced apoptosis of neighboring cells,[52] or decreases cancer-cell apoptosis,[53,54] depending on the system. On the other hand, MMP-7 inhibits apoptosis by cleaving pro-heparin-binding epidermal growth factor (pro-HB-EGF) to generate mature and biologically active HB-EGF that promotes cell survival by stimulating the erb-B4 receptor tyrosine kinase.[55]

MMPs can also promote apoptosis via 'Anoikis', a type of PCD that is induced by inadequate/altered cell matrix interactions.[56,57] Several MMPs are involved in PCD processes through paradoxical contrasting action modes (Table 4). As for example, MMP-11 inhibits cancer-cell apoptosis and its over-expression decreases spontaneous apoptosis in tumor xenografts.[58] Cancer cells injected into MMP-11-null mice have a higher rate of spontaneous apoptosis than in wild-type hosts.[59] However, MMP-11 may inhibit apoptosis by releasing IGFs, which can act as survival factors.[60] Although in animal models MMP-11 decreases cancer-cell apoptosis,[59] it increases apoptosis during tissue remodeling and development.[61] MMP-3 induces apoptosis when over-expressed in epithelial cells, possibly by degrading laminin,[62] but the chronic exposure of tumor cells to stromally derived MMP-3 may promote the selection of tumor epithelial cells that are resistant to apoptosis.[63] It has been observed that MMP-2 and MMP-9 increase apoptosis during tissue remodeling and neoangiogenesis.[64] They also decrease cancer-cell apoptosis by increasing the bioavailability of VEGF and influencing both tumor growth and angiogenesis.[65]

8. MMP inhibitors

The development of synthetic inhibitors of MMPs has relied on the peptide sequence, recognized by the targeted protease, to which have been grafted different chemical functionalities able to interact potently with the zinc ion of the active site.[20] The requirements for a molecule to be an effective inhibitor of the MMP class of enzymes are: (i) a functional group [e.g., hydroxamate ($CONH–O^-$), carboxylate (COO^-), thiolate (S^-), phosphinyl (PO_2^-), etc.] capable of chelating the active-site zinc(II) ion (this will be referred to as zinc binding group or ZBG), (ii) at least one functional group that provides a hydrogen bond interaction with the enzyme backbone, and (iii) one or more side chains, which undergo effective van der Waals interactions with the enzyme subsites.[7] It is now confirmed that these requirements can be satisfied by a variety of different structural classes of MMP inhibitors, which have been discovered by a number of methods including structure-based design[16] and combinatorial chemistry.[66] Some interesting examples for synthetic MMP inhibitors are: marimastat, trocaid, CGS-27023A, prinomastat, AG3340, BAY 12-9566, Ro 32-3555, etc.[1,7]

Natural product MMP inhibitors include tetracyclines, pycnidione, neovastat, squalamine, genistein, nobiletin, myricetin, curcumin, xanthorhizzol, theaflavin, resveratrol, actinonin, BE-166278 (Banyu), matlystatin B, nicotinamide, betulinic acid, glycyrrhetinic acid, rifampicin, catechin derivatives, and a series of futoenone derivatives. It is not very clear how these natural products interact with MMP enzymes. It is possibly due to the presence of a ring hydroxyl and/or carbonyl that chelates the active-site zinc(II) ion. In the case of futoenone derivatives, the replacement of an oxygen substituent by a sulfhydryl group enhances inhibition of stromelysin presumably as a result of stronger zinc(II) ion chelation. Actinonin, BE-166278 (Banyu), and matlystatin B are hydroxamic acid derivatives that bear close structural similarity to similar structures obtained by substrate-based design.[7,67]

9. Structure–activity relationships (SARs)

9.1. Hydroxamates

Most of the MMP inhibitors developed by pharmaceutical companies belong to the hydroxamate category. This choice was actually based on the early studies, which suggest that the extremely potent inhibitors of MMPs can be obtained by grafting a hydroxamate moiety to a suitable peptide sequence.[20] A SAR study for a series of hydroxamic acids (MMP inhibitors) with a quaternary-hydroxyl group at P1 suggested the following[10]:

(a) Stereochemical orientation at P1 is crucial for the activity. For example, compounds bearing 'R' form at P1 were devoid of activity in MMP-3, whereas all the 'S' inhibitors were active.

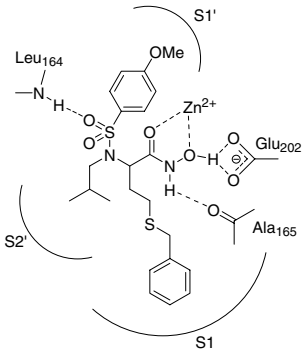


Figure 5. Proposed model of 4-benzylsulfanyl-*N*-hydroxy-2-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyramide in the binding site of MMP-3 from docking simulation. Reprinted with permission from Ref. 68. Copyright 2001 American Chemical Society.

(b) Phenylpropyl group was established as the best substituent at P1 region.
(c) Hydrophobic substituents at P2′ and *N*-methyl amides at P3′ were found to be optimal.

Hanessian et al.[68] have defined successfully the highly hydrophobic S1 pocket, which is surrounded by Tyr-155, His-166, and Tyr-168. The docking simulation of 4-benzylsulfanyl-*N*-hydroxy-2-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyramide in the binding site of MMP-3 has been shown in Figure 5, which indicates that the S1 pocket is occupied by *S*-benzyl group. In an interesting study of the subsite pocket, Okada et al.[69] suggested that a long side chain at P1′ position is preferable for the binding to MMP-2, -3, and -9, and MT1-MMP. An α-branched alkyl group at position P2′ is critical for the binding toward transmembrane domain (ΔMT1), while the introduction of a bulky group at the α-position of hydroxamic acid seems to diminish the activity against ΔMT1.

9.1.1. Phosphonamide-based hydroxamic acids. It has been established that the efficacy of phosphonamide-based hydroxamic acids as MMP inhibitors is mainly dependent on the electronic environments of the phosphorus atom. Thus, the increase in the positive charge on phosphorus atom would certainly affect the rate of the decomposition. Recently, Pikul et al.[70] reported that *N*-hydroxy-2(*R*)-[[(*R*)-methylphenylphosphinyl]-benzylamino]-4-methylpentanamide exhibited potent inhibitory activity against MMPs, and the binding interaction was proposed on the basis of X-ray crystallography data of the inhibitor–enzyme complex as shown in Figure 6. This compound has an additional chiral center at the phosphorus atom different from those of the corresponding sulfonamide derivatives, and it has been found that the stereochemistry at the phosphorus was important for the activity.

On the basis of these findings, Sawa et al.[71] have proposed the following phosphonamide-based inhibitor (Fig. 7) in order to study the SAR and to discover a new class of selective MMP inhibitors.

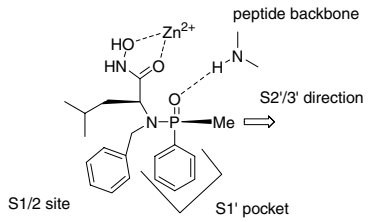


Figure 6. Binding interaction of *N*-hydroxy-2(*R*)-[[(*R*)-methylphenylphosphinyl]-benzylamino]-4-methylpentanamide in MMP enzyme. Reprinted with permission from Ref. 71. Copyright 2002 American Chemical Society.

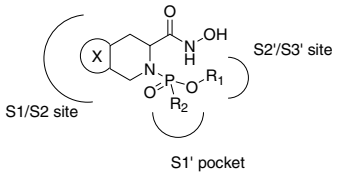


Figure 7. Structure–activity relationships (SARs) for phosphonamide-based hydroxamic acids. Reprinted with permission from Ref. 71. Copyright 2002 American Chemical Society.

The SAR study has shown that the ester group (R_1) seems to have little interaction with the S2′/S3′ site of MMPs, especially of MMP-1. The effects of the substituents R_2 attached to the phosphonamide are important. Introduction of a long alkoxyalkyl chain at the para position of the phenyl ring resulted in the significant decrease of the inhibitory activity against MMP-1, while the inhibitory activities of other enzymes were maintained or increased. Thus, the R_2-substituents would bind to the S1′ pocket of the MMP enzymes, because this pocket is deep for most MMP enzymes, but it is short for MMP-1. On the other hand, bulky substituents at the para position of the phenyl ring increased the inhibitory activity for MMP-9. Insertion of an alkyl chain between the phenyl ring and the phosphonamide moiety resulted in a slight decrease of the inhibitory activity for all enzymes, but the alkenyl chain dramatically decreased the activity for MMP-1. Hydrogen bond (in case of fluorine atom) or a tight bond of the hydroxamate to the zinc ion and the *p*-methoxyphenyl moiety in the S1′ pocket have been mentioned to be obligatory. The oxygen atom of the phosphonamide was positioned at the hydrogen bond distance with the main chain of the Leu-164 and Ala-165. Replacement of 1,2,3,4-tetrahydroisoquinoline ring with other heterocycles provided insight into the structural requirements of the S1/S2 binding site. Regarding the SAR for the X moiety, reduction of the ring size resulted in a significant decrease of the inhibitory activity against all enzymes. Subsequent modeling work strongly supported the presence of *R*-isomer at the phosphorus center.[71]

9.1.2. Cyclophosphinamide and cyclophosphonamide-based hydroxamic acids. An overview of the structure–activity relationships for cyclophosphinamide and cyclophosphonamide-based hydroxamic acids has been shown in Figure 8. These two series of MMP inhibitors were found equally potent in vitro but their SARs were slightly different. The modeling-based binding mode for these two series of MMP inhibitors is shown in Figure 9.[72]

9.1.3. Sulfonamide hydroxamates. The development of first orally available broad-spectrum inhibitor from this class of compounds is CGS 27023A. The key structure of this inhibitor is the isopropyl substituent, which slows down metabolism of the adjacent hydroxamic acid and the basic 3-pyridyl substituent that may aid partitioning

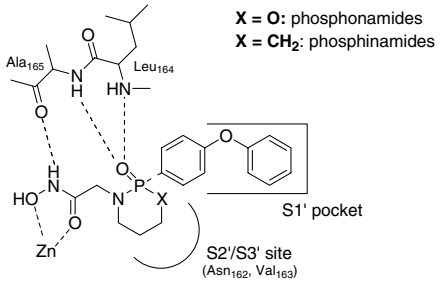


Figure 9. Binding mode of cyclophosphonamide and cyclophosphinamide-based hydroxamic acids in MMP-3. Reprinted with permission from Ref. 72. Copyright 2003 Elsevier.

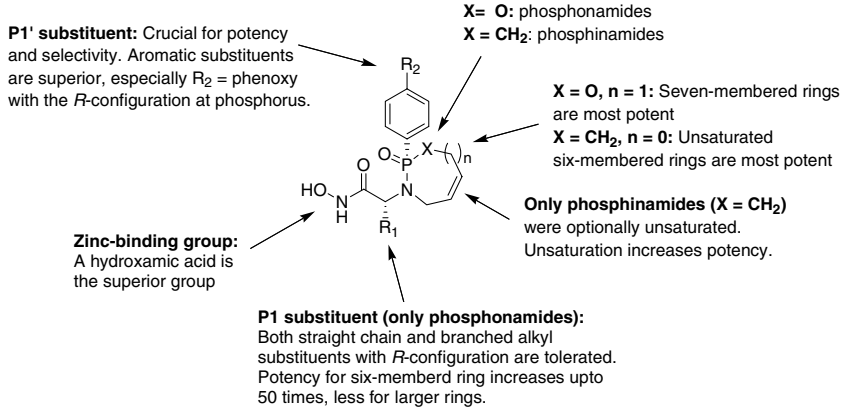


Figure 8. Structure–activity relationships (SARs) for cyclophosphonamide and cyclophosphinamide-based hydroxamic acids. Reprinted with permission from Ref. 72. Copyright 2003 Elsevier.

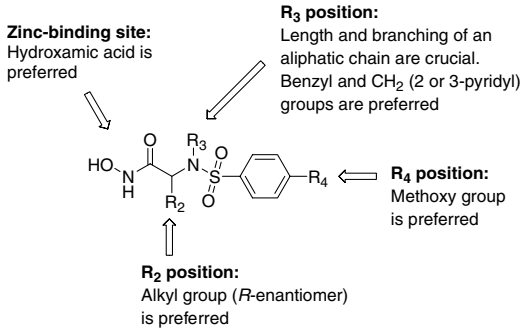


Figure 10. Structure–activity relationships (SARs) for the inhibition of MMP-12 by sulfonamide hydroxamates.

into the hydrated negatively charged environment of cartilage.[7] Structure–activity relationships (SARs) for the inhibition of macrophage metalloelastase (MMP-12) by sulfonamide hydroxamates are shown in Figure 10.[73]

9.2. Nonhydroxamates

On considering the importance of hydroxamic acids as MMP inhibitors, there has also been considerable interest in compounds with alternative zinc binding groups. Most of the MMP inhibitors have been prepared by converting a carboxylic precursor into the corresponding hydroxamic acid. Consequently, a vast volume of test data has been built up on the value of carboxylic acid-containing structures as potential MMP inhibitors. Chapman et al.[74] (Merck Research Laboratories, Rahway, NJ 07065-0900) were among the earliest to disclose MMP inhibitors with an *N*-carboxyalkyl zinc binding group. Now, it has been established that a 3.5 kcal/mol advantage occurs in hydroxamate binding over carboxylate.[16]

9.2.1. Barbiturates. It is well documented that the barbituric acid binds to a zinc atom via interactions with a carbonyl oxygen, a ring nitrogen or a combination of two. Based on the X-ray structure of RS-130830 bound to MMP-13, and the structure-based drug design, the following barbiturate-containing MMP-13 inhibitors have been developed to examine their structure–activity relationships (Fig. 11).[75]

9.2.2. Caffeoyl pyrrolidine derivatives. An overview of the structure–activity relationships for the inhibitory activities of caffeoyl pyrrolidine derivatives on gelatinase (MMP-2 and MMP-9) has been shown in Figure 12.[76]

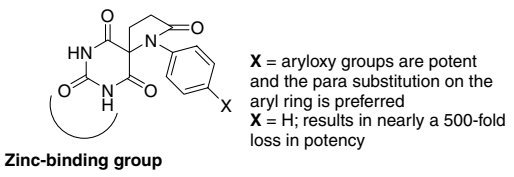


Figure 11. Structure–activity relationships for the inhibition of MMP-13 by barbiturates.

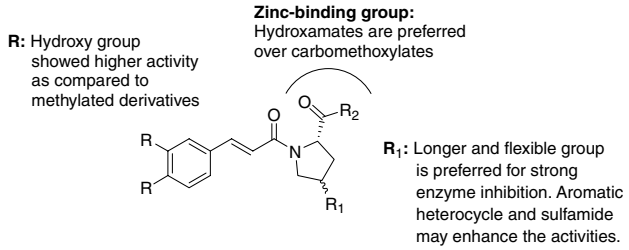


Figure 12. Structure–activity relationships (SARs) for the inhibitory activities of caffeoyl pyrrolidine derivatives on gelatinase (MMP-2 and MMP-9).

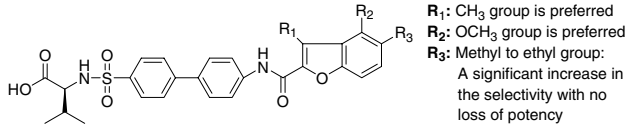


Figure 13. Structure–activity relationships (SARs) for the inhibition of MMP-13 by biphenylsulfonamide carboxylic acids.

9.2.3. Biphenylsulfonamide carboxylic acids. Biphenylsulfonamide carboxylic acids bearing a 3,4,5-tri-substituted benzofuran-2-carboxamide have been found to be potent and highly selective MMP-13 inhibitors. Structure–activity relationships (SARs) for the inhibition of MMP-13 by these compounds are shown in Figure 13.[77]

9.3. Summary of the structure–activity relationships (SARs)

A summary of the structure–activity relationships for the right-hand side and left-hand side MMP inhibitors has been shown in Figures 14 and 15.[7]

10. Quantitative structure–activity relationships (QSARs)

Quantitative structure–activity relationships (QSARs) are one of the well-developed areas in computational chemistry. In the past 44 years, the use of QSAR, since the advent of this methodology,[78] has become increasingly helpful in understanding many aspects of chemical–biological interactions in drug and pesticide research, as well as in the areas of toxicology.[79] This method is useful in elucidating the mechanisms of chemical–biological interaction in various biomolecules, particularly enzymes, membranes, organelles, and cells, as well as in human.[79,80] It has also been utilized for the evaluation of absorption, distribution, metabolism, and excretion (ADME) phenomena in many organisms and whole animal studies.[81] The QSAR approach employs extra-thermodynamically derived and computational-based descriptors to correlate biological activity in isolated receptors, cellular systems, and in vivo. Three standard molecular descriptors routinely used in QSAR analysis: electronic, hydrophobic, and steric, including topological indices, are invaluable in helping to delineate a large number of receptor–ligand interactions that are critical to biological processes.[79] The quality of a QSAR model depends strictly on the type and quality

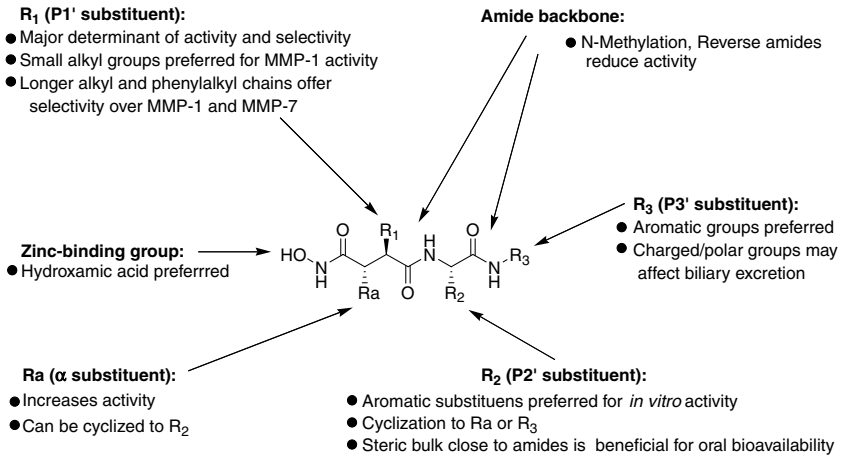


Figure 14. Summary of the structure–activity relationships (SARs) for right-hand side MMP inhibitors. Reprinted with permission from Ref. 7. Copyright 1999 American Chemical Society.

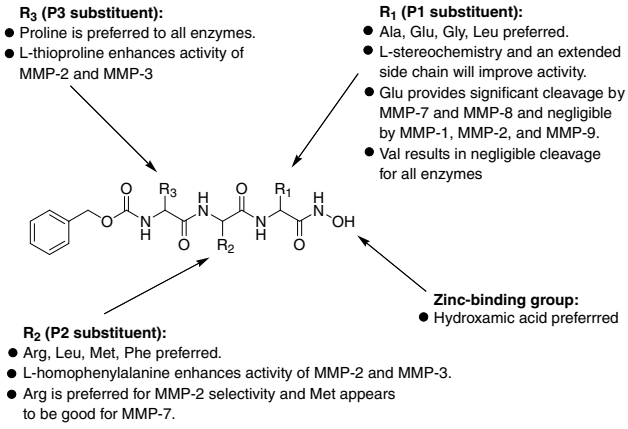


Figure 15. Summary of the structure–activity relationships (SARs) for left-hand side MMP inhibitors.[7]

of the data, and not on the hypotheses, and is valid only for the compound structures analogues to those used to build the model. QSAR models can stand alone to augment other graphical approaches or can be examined in tandem with equations of a similar mechanistic genre to establish their authenticity and reliability.[82] Potential use of QSAR models for screening of chemical databases or virtual libraries before their synthesis appears equally attractive to chemical manufacturers, pharmaceutical companies, and government agencies.

It is important to distinguish between SARs and QSARs: SARs are occurring in the form of structural features that include molecular substructures or fragment counts related to the presence or absence of biological activity; while QSARs are typically quantitative in nature, producing categorical or continuous prediction scales.[83]

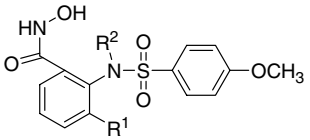
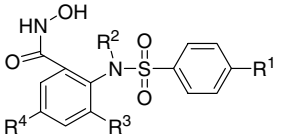
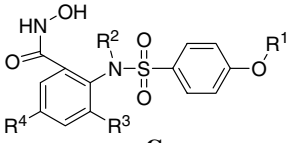
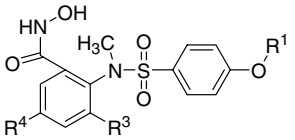
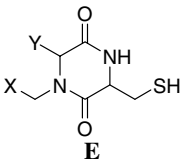
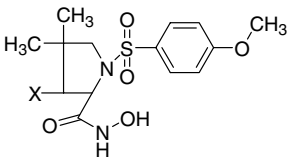
10.1. Review of QSAR studies on MMP inhibitors from the literature

An attempt has been made to collect the QSAR data on MMP inhibitors from the literature, resulting in a total number of 44 QSAR models that are shown in Table 5. The descriptions about the physicochemical parameters, used for the derivation of these QSAR models, are listed in Table 6. The inhibition potency of various compound series against MMP-1, -2, -3, -7, -8, -9, and -13 has been found to be well correlated with a number of physicochemical and structural parameters. The important parameters for these correlations are hydrophobicity, Kier's first-order valence molecular connectivity index ($^1\chi^v$) of the molecule/substituent, electrotopological state (E-state) indices (S*i*) of the atom (*i* = S or N), and polarizability (Pol. or NVE). The most important of these is hydrophobicity, which is one of the most important determinants of inhibitory activity. Out of 44 QSAR, 18 contain a correlation between inhibitory activity and hydrophobicity of the molecule/substituent. A negative linear correlation is found in 14 equations (Eqs. E2–E4, E12, E18, E25–E27, E33, E34, E36, E37, E39, and E43), and the coefficient ranges from −0.062 (Eq. E3) to −1.24 (Eq. E36). Less hydrophobic congeners in these compound families might display enhanced activity. A positive linear correlation is found in only one equation (Eq. E11). This suggests that the activity of this data set might be improved by increasing hydrophobicity of the substituents at ortho and meta positions. Parabolic correlations with hydrophobicity are found in three equations (Eqs. E1, E13, and E28), which reflect situations where activity declines with increasing hydrophobicity and then changes direction and increases. It may correspond to an allosteric reaction.[91–99]

10.2. Evaluation of new QSAR on MMP inhibitors

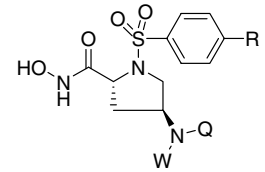
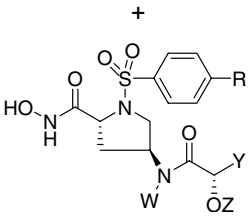
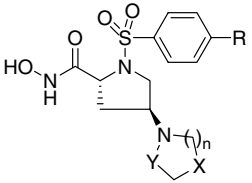
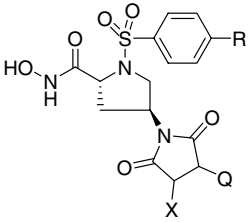
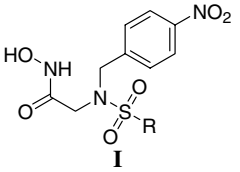
10.2.1. Materials and methods. All the data have been collected from the literature (see individual QSAR for respective references). IC_{50} is the 50% inhibitory concentration of a compound, which is expressed in molar concentration. Similarly, K_i is the inhibitory constant of a compound and is also expressed in molar concentration. $\log 1/IC_{50}$ and $\log 1/K_i$ are the dependent variables, which define the biological parameter for QSAR equations. Physicochemical descriptors are auto-loaded, and multi-regression analyses (MRA) used to derive

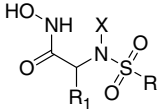
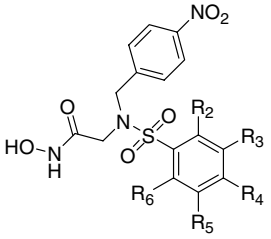
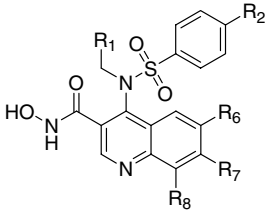
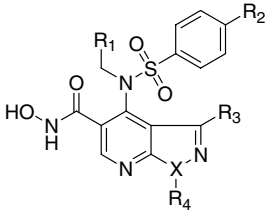
Table 5. QSAR results on MMP inhibitors obtained from the literature

En	MMP type	Structure	QSAR equation	Statistics	Ref.
E1	MMP-1	 **A**	$\log(1/IC_{50}) = -2.473(\pm1.279)\log P + 1.098(\pm0.683)(\log P)^2 + 7.286(\pm0.331)$	$n = 7$, $r = 0.960$, $r^2_{cv} = 0.80$, $s = 0.18$, $F_{1,4} = 23.53(21.20)$, $\log P_o = 1.13$	84
E2	MMP-1	 **B**	$\log(1/IC_{50}) = -0.192(\pm0.118)\log P + 1.020(\pm0.396)I_2 + 0.596(\pm0.487)I_3 + 5.979(\pm0.432)$ $I_2 = 1$ for $R^2 = CH_2$-3-pyridyl, otherwise $I_2 = 0$; $I_3 = 1$ for R^3 = an aromatic substituent, otherwise $I_3 = 0$	$n = 16$, $r = 0.919$, $r^2_{cv} = 0.67$, $s = 0.28$, $F_{3,12} = 21.86(5.95)$	84
E3	MMP-1	 **C**	$\log(1/IC_{50}) = 0.534(\pm0.251)I_1 + 0.629(\pm0.173)I_2 + 0.317(\pm0.186)I_3 + 0.234(\pm0.147)I_{4,Br} - 0.062(\pm0.060)\log P + 6.801(\pm0.150)$ $I_1 = 1$ for R^1 = Ph-4-Cl, otherwise $I_1 = 0$; $I_2 = 1$ for R^2 = nitrogen-containing group, otherwise $I_2 = 0$; $I_3 = 1$ for $R^3 = CH_2N[(CH_2)_2]_2NCH_3$, otherwise $I_3 = 0$; $I_{4,Br} = 1$ for R^4 = Br, otherwise $I_4 = 0$	$n = 19$, $r = 0.935$, $r^2_{cv} = 0.74$, $s = 0.13$, $F_{5,13} = 18.15(4.86)$	84
E4	MMP-1	 **D**	$\log(1/IC_{50}) = -0.596(\pm0.234)\log P + 7.276(\pm0.549)$	$n = 9$, $r = 0.916$, $r^2_{cv} = 0.67$, $s = 0.22$, $F_{1,7} = 36.46(12.25)$	84
E5	MMP-1	 **E**	$\log 1/C = 0.038(\pm0.011)$ NVE + 1.85(±1.22)	$n = 6$, $r^2 = 0.956$, $s = 0.076$, $q^2 = 0.887$	85
E6	MMP-1	 **F**	$\log 1/C = 0.034(\pm0.014)$ NVE + 0.24(±2.2)	$n = 6$, $r^2 = 0.922$, $s = 0.239$, $q^2 = 0.810$	85

(*continued on next page*)

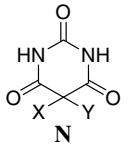
Table 5 (*continued*)

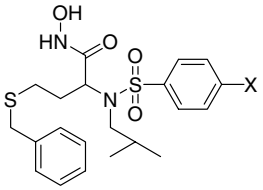
En	MMP type	Structure	QSAR equation	Statistics	Ref.
E7	MMP-1	 **Ga** +  **Gb**  **Ha**	$\log(1/IC_{50}) = -0.286(\pm0.166)^{1}\chi^{v}_{R} + 0.748(\pm0.309)I_W + 6.775(\pm0.268)$ If W = H, $I_W = 0$, otherwise $I_W = 1$	$n = 19$, $r = 0.901$, $r^2_{cv} = 0.63$, $s = 0.23$, $F_{2,16} = 34.71(6.23)$, $R^2_A = 0.79$	86
E8	MMP-1	+  **Hb**	$\log(1/IC_{50}) = -4.721(\pm1.093)^{1}\chi^{v}_{R} + 1.858(\pm0.387)(^{1}\chi^{v}_{R})^2 + 5.678(\pm2.511)S_S + 1.444(\pm0.712)I_Y + 42.213(\pm14.811)$ If Y = CH_2, $I_Y = 0$, and if Y = SO_2 or CO, $I_Y = 1$	$n = 26$, $r = 0.933$, $r^2_{cv} = 0.78$, $s = 0.27$, $F_{4,21} = 35.36(4.37)$, $R^2_A = 0.85$	86
E9	MMP-1	 **I**	$\log(1/K_i) = 0.198(\pm0.122)S_N + 0.893(\pm0.259)D + 7.441(\pm0.114)$ If R = C_6F_5 or 3-CF_3–C_6H_4, $D = 1$, otherwise $D = 0$	$n = 28$, $r = 0.830$, $s = 0.17$, $F_{2,25} = 27.67(5.57)$, $R^2_A = 0.66$	87

E10	MMP-1	 **J**	$\log(1/K_i) = 0.194(\pm0.082)\,{}^1\chi^v + 0.423(\pm0.144)\,S_S - 0.862(\pm0.242)\,S_N + 0.750(\pm0.142)\,I + 8.859(\pm1.614)$ $I = 1$ for R = C_6F_5, otherwise $I = 0$	$n = 31$, $r = 0.945$, $s = 0.17$, $F_{4,26} = 53.78(4.14)$, $R^2 = 0.876$	88
E11	MMP-1	 **K**	$pC_1 = 0.550(\pm0.264)\,\pi_{o+m} - 0.576(\pm0.332)\,I_{vic} + 0.587(\pm0.367)\,\sigma_m - 0.634(\pm0.383)\,MR_o + 1.752(\pm0.482)$ $I_{vic} = 1$, if substituents having size larger than that of hydrogen are present on vicinal carbon atoms of the phenyl ring, and 0, otherwise	$n = 19$, $R = 0.878$, SEE = 0.172, $F_{4,14} = 11.8$	89
E12	MMP-1	 **L**	$\log(1/IC_{50}) = -0.176(\pm0.136)\,\mathrm{Clog}\,P + 0.840(\pm0.292)I_{2,M} + 6.576(\pm0.597)$ $I_{2,M} = 1$ for $R_2 = OCH_3$, otherwise $I_{2,M} = 0$	$n = 19$, $r = 0.914$, $r^2_{cv} = 0.73$, $s = 0.21$, $F_{2,16} = 40.75(6.23)$	90
E13	MMP-1	 **M**	$\log(1/IC_{50}) = -2.116(\pm0.882)\,\mathrm{Clog}\,P + 0.928(\pm0.372)\,(\mathrm{Clog}\,P)^2 + 0.462(\pm0.408)I_{1,pyr} + 6.895(\pm0.588)$ $I_{1,pyr} = 1$ for R_1 = 3-pyridyl group, otherwise $I_{1,pyr} = 0$	$n = 10$, $r = 0.954$, $r^2_{cv} = 0.71$, $s = 0.24$, $F_{3,6} = 20.12(9.78)$, $\mathrm{Clog}\,P_0 = 1.14$	90
E14	MMP-2	**Ga** + **Gb**	$\log(1/IC_{50}) = 0.202(\pm0.106)\,{}^1\chi^v_N + 8.369(\pm0.414)$	$n = 9$, $r = 0.863$, $r^2_{cv} = 0.56$, $s = 0.23$, $F_{1,7} = 20.46(12.25)$, $R^2_A = 0.71$	86
E15	MMP-2	**Ha** + **Hb**	$\log(1/IC_{50}) = -1.965(\pm0.823)S_S - 0.217(\pm0.195)\,{}^1\chi^v_N - 2.195(\pm4.679)$	$n = 9$, $r = 0.926$, $r^2_{cv} = 0.76$, $s = 0.15$, $F_{2,6} = 18.18(10.92)$, $R^2_A = 0.81$	86
E16	MMP-2	**I**	$\log(1/K_i) = -1.172(\pm0.489)\,S_N + 0.432(\pm0.312)\,S_S + 0.149(\pm0.082)\,{}^1\chi^v\ 0.898(\pm0.207)D + 9.447(\pm1.052)$ If R = C_6F_5 or 3-CF_3-C_6H_4, $D = 1$, otherwise $D = 0$	$n = 33$, $r = 0.928$, $s = 0.19$, $F_{2,28} = 43.47(4.07)$, $R^2_A = 0.84$	87
E17	MMP-2	**J**	$\log(1/K_i) = 0.204(\pm0.080)\,{}^1\chi^v + 0.198(\pm0.127)\,S_S - 0.682(\pm0.211)\,S_N + 0.616(\pm0.144)\,I + 7.938(\pm1.563)$ $I = 1$ for R = C_6F_5, otherwise $I = 0$	$n = 31$, $r = 0.964$, $s = 0.21$, $F_{4,34} = 111(3.93)$, $R^2 = 0.921$	88
E18	MMP-2	**K**	$pC_2 = 5.695(\pm1.852)\sigma_m - 5.499(\pm2.404)\sigma^2_m - 1.515(\pm0.622)MR_m - 0.362(\pm0.333)\pi_o + 2.158(\pm0.550)$	$n = 18$, $R = 0.911$, SEE = 0.202, $F_{4,13} = 15.9$	89
E19	MMP-3	**Ga** + **Gb**	$\log(1/IC_{50}) = -0.501(\pm0.206)\,{}^1\chi^v_N + 0.050(\pm0.029)({}^1\chi^v_N)^2 + 0.656(\pm0.218)I_W - 2.946(\pm0.945)S_S - 7.850(\pm5.066)$ If W = H, $I_W = 0$, otherwise $I_W = 1$	$n = 20$, $r = 0.916$, $r^2_{cv} = 0.65$, $s = 0.18$, $F_{4,15} = 19.58(4.89)$, $R^2_A = 0.80$	86

(*continued on next page*)

Table 5 (*continued*)

En	MMP type	Structure	QSAR equation	Statistics	Ref.
E20	MMP-3	**Ha** + **Hb**	$\log(1/IC_{50}) = -0.137(\pm0.080)^1\chi^v_N + 0.561(\pm0.177)I_R + 7.864(\pm0.278)$ $I_R = 1$ for all R-substituents except R = $OCH_2CH_2OCH_3$ for which it is zero	$n = 26$, $r = 0.843$, $r^2_{cv} = 0.63$, $s = 0.14$, $F_{2,23} = 28.27(5.66)$, $R^2_A = 0.69$	86
E21	MMP-7	**Ga** + **Gb**	$\log(1/IC_{50}) = 0.175(\pm0.084)^1\chi^v_N + 0.405(\pm0.234)I_W + 1.863(\pm0.982)S_S + 15.319(\pm5.224)$ If W = H, $I_W = 0$, otherwise $I_W = 1$	$n = 12$, $r = 0.866$, $r^2_{cv} = 0.47$, $s = 0.10$, $F_{3,8} = 8.01(7.59)$, $R^2_A = 0.66$	86
E22	MMP-7	**Ha** + **Hb**	$\log(1/IC_{50}) = 1.843(\pm1.541)^1\chi^v_N - 0.274(\pm0.247)(^1\chi^v_N)^2 - 1.709(\pm1.025)^1\chi^v_R + 0.743(\pm0.348)(^1\chi^v_R)^2 - 1.811(\pm0.931)S_S + 0.928(\pm0.346)I_R - 7.950(\pm5.200)$ $I_R = 1$ for all R-substituents except R = $OCH_2CH_2OCH_3$ for which it is zero.	$n = 27$, $r = 0.903$, $r^2_{cv} = 0.68$, $s = 0.25$, $F_{6,20} = 14.71(3.87)$, $R^2_A = 0.76$	86
E23	MMP-8	**I**	$\log(1/K_i) = -0.466(\pm0.172)S_N + 0.909(\pm0.300)D + 8.205(\pm0.163)$ If R = C_6F_5 or 3-CF_3–C_6H_4, $D = 1$, otherwise $D = 0$	$n = 31$, $r = 0.844$, $s = 0.24$, $F_{2,28} = 34.64(5.45)$, $R^2_A = 0.69$	87
E24	MMP-8	**J**	$\log(1/K_i) = 0.244(\pm0.118)^1\chi^v + 0.264(\pm0.194)S_S - 0.757(\pm0.320)S_N + 0.667(\pm0.219)I + 7.933(\pm2.366)$ $I = 1$ for R = C_6F_5, otherwise $I = 0$	$n = 37$, $r = 0.940$, $s = 0.31$, $F_{4,32} = 60.20(3.97)$, $R^2 = 0.869$	88
E25	MMP-8	**K**	$pC_8 = 7.676(\pm2.222)\sigma_m - 6.572(\pm2.884)\sigma^2_m - 2.573(\pm0.747)MR_m - 0.461(\pm0.397)\pi_o + 2.342(\pm0.659)$	$n = 18$, $R = 0.939$, SEE = 0.242, $F_{4,13} = 24.4$	89
E26	MMP-9	**A**	$\log(1/IC_{50}) = -0.576(\pm0.147)\log P + 8.525(\pm0.193)$	$n = 10$, $r = 0.954$, $r^2_{cv} = 0.86$, $s = 0.15$, $F_{1,8} = 81.56(11.26)$	84
E27	MMP-9	**B**	$\log(1/IC_{50}) = -0.265(\pm0.183)\log P - 1.241(\pm0.725)I_1 + 1.183(\pm0.691)I_4 + 8.336(\pm0.492)$ $I_1 = 1$ for $R^1 = OCH_2Ph$, otherwise $I_1 = 0$; $I_4 = 1$ for R^4 = an aromatic moiety, otherwise $I_4 = 0$	$n = 19$, $r = 0.882$, $r^2_{cv} = 0.64$, $s = 0.50$, $F_{3,15} = 17.47(5.42)$	84
E28	MMP-9	**C**	$\log(1/IC_{50}) = 0.695(\pm0.172)I_3 - 0.154(\pm0.133)\log P + 0.064(\pm0.039)(\log P)^2 + 8.143(\pm0.122)$ $I_3 = 1$ for $R^3 = CH_2N[(CH_2)_2]_2NCH_3$, otherwise $I_3 = 0$	$n = 19$, $r = 0.931$, $r^2_{cv} = 0.74$, $s = 0.16$, $F_{2,16} = 32.65(6.23)$, $\log P_o = 1.20$	84
E29	MMP-9	**D**	$\log(1/IC_{50}) = 0.503(\pm0.477)Pol - 1.806(\pm0.567)I_{1,CC} - 0.807(\pm0.559)I_{1,N} + 5.916(\pm2.137)$ $I_{1,CC} = 1$ for R^1 = acetylene-derived substituents, otherwise $I_{1,CC} = 0$; $I_{1,N} = 1$ for R^1 = nitrogen-containing substituents, otherwise $I_{1,N} = 0$	$n = 16$, $r = 0.920$, $r^2_{cv} = 0.64$, $s = 0.37$, $F_{3,12} = 21.94(5.95)$	84
E30	MMP-9		$\log 1/C = 0.037(\pm0.013)$ NVE + 2.04(±1.70)	$n = 7$, $r^2 = 0.911$, $s = 0.318$, $q^2 = 0.843$	85
E31	MMP-9	**I**	$\log(1/K_i) = -1.249(\pm0.618)S_N + 0.512(\pm0.394)S_S + 0.166(\pm0.103)^1\chi^v + 1.057(\pm0.262)D + 9.581(\pm1.332)$ If R = C_6F_5 or 3-CF_3–C_6H_4, $D = 1$, otherwise $D = 0$	$n = 33$, $r = 0.902$, $s = 0.23$, $F_{4,28} = 30.50(4.07)$, $R^2_A = 0.79$	87
E32	MMP-9	**J**	$\log(1/K_i) = 0.283(\pm0.106)^1\chi^v + 0.433(\pm0.143)S_N + 0.683(\pm0.240)I + 5.510(\pm0.951)$ $I = 1$ for R = C_6F_5, otherwise $I = 0$	$n = 37$, $r = 0.920$, $s = 0.34$, $F_{3,33} = 60.70(4.44)$, $R^2 = 0.832$	88
E33	MMP-9	**K**	$pC_9 = 6.581(\pm2.173)\sigma_m - 6.302(\pm2.820)\sigma^2_m - 1.796(\pm0.730)MR_m - 0.526(\pm0.390)\pi_o + 2.161(\pm0.645)$	$n = 18$, $R = 0.910$, SEE = 0.237, $F_{4,13} = 15.7$	89

E34	MMP-9	**L**	$\log(1/IC_{50}) = -0.161(\pm0.153)\text{Clog}\,P + 1.391(\pm0.440)I_{2,M} - 0.461(\pm0.414)I_6 - 0.619(\pm0.312)I_7 + 7.680(\pm0.747)$ $I_{2,M} = 1$ for $R_2 = OCH_3$, otherwise $I_{2,M} = 0$; $I_6 = 1$ for R_6 = a halogen or halogen-containing group, otherwise $I_6 = 0$; $I_7 = 1$ for R_7 = a halogen or halogen-containing group, otherwise $I_7 = 0$	$n = 18$, $r = 0.945$, $r^2_{cv} = 0.60$, $s = 0.25$, $F_{4,13} = 27.28(5.20)$	90
E35	MMP-9	**M**	$\log(1/IC_{50}) = 2.192(\pm0.340)\text{Pol} - 0.866(\pm0.256)I_{2,CC} - 2.077(\pm1.603)$ $I_{2,CC} = 1$ for R_2 = butynyloxy group, otherwise $I_{2,CC} = 0$	$n = 10$, $r = 0.991$, $r^2_{cv} = 0.95$, $s = 0.15$, $F_{2,7} = 199.82(9.55)$	90
E36	MMP-13	**A**	$\log(1/IC_{50}) = -1.240(\pm0.247)\log P + 8.699(\pm0.302)$	$n = 9$, $r = 0.976$, $r^2_{cv} = 0.92$, $s = 0.23$, $F_{1,7} = 140.93(12.25)$	84
E37	MMP-13	**B**	$\log(1/IC_{50}) = -0.184(\pm0.138)\log P - 1.051(\pm0.552)I_1 + 1.079(\pm0.626)I_3 + 1.341(\pm0.527)I_4 + 7.902(\pm0.366)$ $I_1 = 1$ for $R^1 = OCH_2Ph$, otherwise $I_1 = 0$; $I_3 = 1$ for R^3 = an aromatic substituent, otherwise $I_3 = 0$; $I_4 = 1$ for R^4 = an aromatic moiety, otherwise $I_4 = 0$	$n = 22$, $r = 0.919$, $r^2_{cv} = 0.75$, $s = 0.38$, $F_{4,17} = 23.06(4.67)$	84
E38	MMP-13	**C**	$\log(1/IC_{50}) = 0.410(\pm0.158)\text{Pol} + 0.773(\pm0.325)I_1 + 5.960(\pm0.824)$ $I_1 = 1$ for R^1 = Ph-4-Cl, otherwise $I_1 = 0$	$n = 19$, $r = 0.914$, $r^2_{cv} = 0.79$, $s = 0.19$, $F_{2,14} = 40.71(6.51)$	84
E39	MMP-13	**D**	$\log(1/IC_{50}) = -0.320(\pm0.192)\log P - 0.891(\pm0.422)I_{1,CC} - 0.531(\pm0.403)I_{1,N} + 8.220(\pm0.467)$ $I_{1,CC} = 1$ for R^1 = acetylene-derived substituents, otherwise $I_{1,CC} = 0$; $I_{1,N} = 1$ for R^1 = nitrogen-containing substituents, otherwise $I_{1,N} = 0$	$n = 17$, $r = 0.910$, $r^2_{cv} = 0.70$, $s = 0.29$, $F_{3,13} = 20.78(5.74)$	84
E40	MMP-13	 **O**	$\log 1/C = 0.025(\pm0.011)\text{NVE} + 3.73(\pm1.95)$	$n = 4$, $r^2 = 0.980$, $s = 0.058$, $q^2 = 0.925$	85
E41	MMP-13	**Ga + Gb**	$\log(1/IC_{50}) = 0.065(\pm0.054)^1\chi^v_N + 0.379(\pm0.124)^1\chi^v_R + 0.535(\pm0.211)I_W + 8.098(\pm0.269)$ If W = H, $I_W = 0$, otherwise $I_W = 1$	$n = 18$, $r = 0.900$, $r^2_{cv} = 0.72$, $s = 0.15$, $F_{3,14} = 19.87(5.56)$, $R^2_A = 0.77$	86
E42	MMP-13	**Ha + Hb**	$\log(1/IC_{50}) = 1.158(\pm0.964)^1\chi^v_N - 0.187(\pm0.151)(^1\chi^v_N)^2 - 0.799(\pm0.487)S_S + 0.871(\pm0.213)I_R + 2.102(\pm3.042)$ $I_R = 1$ for all R-substituents except R = $OCH_2CH_2OCH_3$ for which it is zero	$n = 20$, $r = 0.915$, $r^2_{cv} = 0.73$, $s = 0.14$, $F_{4,15} = 19.38(4.89)$, $R^2_A = 0.79$	86
E43	MMP-13	**L**	$\log(1/IC_{50}) = -0.396(\pm0.114)\text{Clog}\,P + 9.691(\pm0.382)$	$n = 18$, $r = 0.879$, $r^2_{cv} = 0.73$, $s = 0.21$, $F_{1,16} = 54.63(8.53)$	90
E44	MMP-13	**M**	$\log(1/IC_{50}) = 1.730(\pm0.596)\text{Pol} - 1.106(\pm0.449)I_{2,CC} - 0.233(\pm2.810)$ $I_{2,CC} = 1$ for R_2 = butynyloxy group, otherwise $I_{2,CC} = 0$	$n = 10$, $r = 0.971$, $r^2_{cv} = 0.88$, $s = 0.26$, $F_{2,7} = 56.77(9.55)$	90

E*n* is the number of the published equations (where, $n = 1, 2, 3, \ldots, 44$). IC_{50} or *C* refers to the molar concentration of the compounds leading to 50% inhibition of the enzyme. K_i represents the inhibition constant of compounds for the enzyme. pC_1, pC_2, pC_8, and pC_9 are the activities of compounds against MMP-1, -2, -8, and -9, respectively. *n* is the number of data points, *r* or *R* is the correlation coefficient, r^2_{cv} is the square of cross-validates correlation coefficient obtained by leave-one-out jackknife procedure, *s* is the standard deviation, and *F* is the *F*-ratio between the variances of calculated and observed activities (within parentheses the figure refers to the *F* value at 90% 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. R^2_A or R^2 is the adjusted value of r^2 defined as $R^2_A = r^2(1 - 1/F)$. R^2_A is also known as explained variance (EV), which, when multiplied by 100, gives what percent of the variance in activity can be accounted for by the equations. SEE is the standard error of estimate.

Table 6. Description about the physicochemical parameters used for the QSAR models listed in Table 5

No.	Physicochemical parameter	Description
1	$\log P$ or Clog P	Hydrophobicity of the molecules
2	$\log P_o$	Optimum value of hydrophobicity for the molecules
3	π	Hydrophobicity of the substituents
4	NVE	Number of valence electron
5	$^1\chi^v$	Kier's first-order valence molecular connectivity index ($^1\chi^v$) of the substituents/molecules
6	S_i	Electrotopological state (E-state) indices (S_i) of the atom: measure of the availability of π or lone pair electrons on the atom
7	S_N	(E-state) indices nitrogen atom: availability of π or lone pair electrons on the nitrogen atom.
8	S_S	(E-state) indices sulfur atom: availability of π or lone pair electrons on the sulfur atom.
9	σ	Sigma (electronic parameter)
10	MR	Molar refractivity
11	Pol	Polarizability

the QSAR are executed with the C-QSAR program.[100] The parameters used in this review have already been discussed in detail along with their application.[79] Briefly, Clog P is the calculated partition coefficient in *n*-octanol/water and is a measure of hydrophobicity, and π is the hydrophobic parameter for substituents. Cπ is the calculated hydrophobic parameter of the substituents. σ, σ^+, and σ^- are Hammett electronic parameters that apply to substituent effects on aromatic systems. $B1$, $B5$, and L are Verloop's sterimol parameters for substituents.[101] $B1$ is a measure of the minimum width of a substituent, $B5$ is an attempt to define maximum width of the whole substituent, and L is the substituent length.

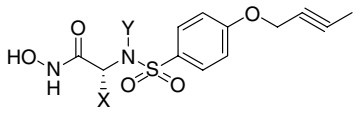
CMR is the calculated molar refractivity for the whole molecule. MR is calculated from the Lorentz–Lorenz equation and is described as follows: $[(n^2-1)/(n^2+2)](MW/\delta)$, where n is the refractive index, MW is the molecular weight, and δ is the density of the substance. MR is dependent on volume and polarizability. It can be used for a substituent or for the whole molecule. A new polarizability parameter, NVE, was developed, which is shown to be effective at delineating various chemico-biological interactions.[85,102–104] NVE represents the total number of valence electrons and is calculated by simply summing up the valence electrons in a molecule, that is, H = 1, C = 4, Si = 4, N = 5, P = 5, O = 6, S = 6, and halogens = 7. It may also be represented as: $NVE = n_\sigma + n_\pi + n_n$, where n_σ is the number of electrons in σ-orbital, n_π is the number of electrons in π-orbitals, and n_n is the number of lone pair electrons. MgVol is the molar volume for the whole molecule.[105] The indicator variable I is assigned the value of 1 or 0 for special features with special effects that cannot be parametrized and has been explained wherever used.

In QSAR equations, n is the number of data points, r is the correlation coefficient between observed values of the dependent and the values calculated from the equation, r^2 is the square of the correlation coefficient representing the goodness of fit, q^2 is the cross-validated r^2 (a measure of the quality of the QSAR model), and s is the standard deviation. The cross-validated r^2 (q^2) is obtained by using leave-one-out (LOO) procedure as described by Cramer et al.[106] Q is the quality factor (quality ratio), where $Q = r/s$. Chance correlation, due to the excessive number of parameter (which increases the r and s values also), can, thus, be detected by the examination of Q value. F is the Fischer statistics (Fischer ratio), $F = fr^2/[(1-r^2)m]$, where f is the number of degree of freedom, $f = n-(m+1)$, n is the number of data points and m is the number of variables. The modeling was taken to be optimal when Q reached a maximum together with F, even if slightly nonoptional F values have normally been accepted. A significant decrease in F with the introduction of one additional variable (with increasing Q and decreasing s) could mean that the new descriptor is not as good as expected, that is, its introduction has endangered the statistical quality of the combination that nevertheless can again improve with the ulterior introduction of a more convincing descriptor.[107] Compounds were assigned to be outliers on the basis of their deviation between observed and calculated activities from the equation (>2s).[108] Each regression equation includes 95% confidence limits for each term in parentheses.

All the new QSARs reported here are derived by us and were not formulated by the original authors. These QSARs are found to be statistically significant, which fulfill the conditions given by Golbraikh and Tropsha[109] as the acceptable models. These models also fulfill the condition of (number of data points)/(number of descriptors) $\geqslant 4$. For a list of outliers in each data set, refer to the corresponding tables.

10.2.2. Results and discussion

10.2.2.1. MMP-1 inhibitors. *Inhibition of MMP-1 by acyclic α-sulfonamide hydroxamates (**I**).* Data obtained from Levin et al.[110] (Table 7).



I

$$\log 1/IC_{50} = 0.94(\pm 0.39)\text{Clog}P - 1.01(\pm 0.46)I_Y + 4.72(\pm 0.88), \quad (1)$$

$n = 13$, $r^2 = 0.849$, $s = 0.369$, $q^2 = 0.727$, $Q = 2.499$, $F = 28.113$.

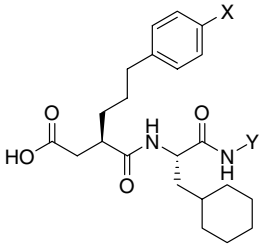
Table 7. Biological, physicochemical, and structural parameters used to derive QSAR equations 1 and 32 for the inhibition of MMP-1 and MMP-9, respectively, by acyclic α-sulfonamide hydroxamates (**I**)

No.	X	Y	D/L	$\log 1/IC_{50}$ (Eq. 1)			$\log 1/IC_{50}$ (Eq. 32)			Clog *P*	$C\pi_X$	I_Y
				Obsd.	Pred.	*Δ*	Obsd.	Pred.	*Δ*			
1	H	H	D	—	—	—	6.12	6.02	0.10	0.86	0.00	1
2[b]	H	CH_3	D	5.72	5.92	−0.20	6.51	7.34	−0.83	1.28	0.00	0
3	H	CH_2-3-pyridyl	D	5.94	6.11	−0.17	7.40	7.34	0.06	1.48	0.00	0
4	CH_3	H	D	5.39	4.81	0.58	6.10	6.16	−0.06	1.17	0.31	1
5	CH_3	CH_3	D	6.48	6.21	0.27	7.17	7.49	−0.32	1.59	0.31	0
6[b]	$CH(CH_3)_2$	H	D	5.53	5.68	−0.15	7.38	6.61	0.77	2.10	1.24	1
7	$CH(CH_3)_2$	CH_3	D	6.59	7.08	−0.49	7.96	7.93	0.03	2.51	1.24	0
8	$C(CH_3)_3$	H	D	6.06	6.05	0.01	6.65	6.80	−0.15	2.50	1.64	1
9	$(CH_3)_2$	H	D	5.00	5.10	−0.10	5.86	6.16	−0.30	1.48	0.31	1
10[a]	$CH(CH_3)OH$	H	D	5.61	4.15	1.46	6.11	5.83	0.28	0.47	−0.39	1
11	CH_2SCH_2-3-pyridyl	H	D,L	5.72	5.56	0.16	6.80	6.55	0.25	1.97	1.11	1
12	CH_2SCH_2-3-pyridyl	CH_3	D,L	7.21	7.00	0.21	7.85	7.87	−0.02	2.43	1.11	0
13	$C(CH_3)_2SCH_2$-3-pyridyl	H	D,L	6.32	6.22	0.10	6.89	6.89	0.00	2.68	1.82	1
14	$C(CH_3)_2SCH_2$-3-pyridyl	CH_3	D,L	8.05	7.66	0.39	8.40	8.21	0.19	3.14	1.82	0
15	C_6H_4-4-$O(CH_2)_2NHCH_3$	H	D	5.00	5.61	−0.61	6.46	6.57	−0.11	2.02	1.16	1
16[a]	C_6H_4-4-$O(CH_2)_2NHCH_3$	CH_3	D	6.03	7.01	−0.98	7.96	7.90	0.06	2.44	1.16	0

[a] Not included in the derivation of QSAR 1.
[b] Not included in the derivation of QSAR 32.

Two compounds in Table 7 were deemed to be outliers on the basis of their deviations (>2*s*). Clog *P* is the most significant term, followed by an indicator variable (I_Y). Positive Clog *P* suggests that highly hydrophobic acyclic α-sulfonamide hydroxamates (**I**) would be more active. Thus, the most active compound in Table 7 (compound **13**; $\log 1/IC_{50} = 8.05$) having the highest value of hydrophobicity (Clog *P* = 3.14). The indicator variable (I_Y) applies to those compounds, which have Y = H. The negative coefficient of the indicator variable indicates that the presence of methyl or CH_2-3-pyridyl groups at Y-position will improve the activity. It can be seen by comparing the activities of those molecules, which differ only due to the value of Y, that is, Y = H or CH_3. Such types of compounds are 3 and 4, 5 and 6, 10 and 11, 12 and 13, and 14 and 15 of Table 7.

*Inhibition of MMP-1 by analogues (**II**)*. Data obtained from Terp et al.[111] (Table 8).



II

$$\log 1/K_i = 0.22(\pm 0.07)\text{Clog}P + 3.25(\pm 0.38), \quad (2)$$

$n = 11$, $r^2 = 0.827$, $s = 0.117$, $q^2 = 0.731$, $Q = 7.769$, $F = 43.023$.

Hydrophobicity is found to be the single most important parameter for this data set, which shows that at all the parts where substituents have been entered, hydrophobic

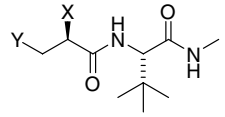
Table 8. Biological and physicochemical parameters used to derive QSAR equation 2 for the inhibition of MMP-1 by analogues (**II**)

No.	X	Y	$\log 1/K_i$ (Eq. 2)			Clog *P*
			Obsd.	Pred.	*Δ*	
1	H	$(CH_2)_2C_6H_5$(RS)	4.68	4.60	0.08	6.29
2	H	$(CH_2)_2C_6H_5$(SS)	4.70	4.60	0.10	6.29
3	H	$(CH_2)_2CH_4$-4-SO_2NH_2	4.40	4.21	0.19	4.45
4	H	$(CH_2)_2CO_2Me$	4.24	4.27	−0.03	4.76
5[a]	H	$(CH_2)_3CONH_2$	4.55	4.08	0.47	3.86
6	Me	$(CH_2)_2C_6H_5$	4.66	4.71	−0.05	6.79
7	Me	$(CH_2)_2C_6H_4$-4-SO_2NH_2	4.32	4.32	0.00	4.95
8	OMe	$(CH_2)_2C_6H_4$-4-SO_2NH_2	4.00	4.19	−0.19	4.37
9	Cl	$(CH_2)_2C_6H_4$-4-SO_2NH_2	4.26	4.36	−0.10	5.17
10	Me	$(CH_2)_2CO_2Me$	4.38	4.38	0.00	5.26
11[a]	Me	$(CH_2)_2COOH$	4.00	4.28	−0.28	4.79
12	Me	$(CH_2)_4$-morpholinyl	4.00	3.89	0.11	2.95
13	H	H	4.00	4.10	−0.10	3.93

[a] Not included in the derivation of QSAR 2.

contacts have been made. The linear Clog *P* model suggests that the highly hydrophobic molecules will be more active. Eq. 2 explains 82.7% of variance in $\log 1/K_i$.

*Inhibition of human fibroblast collagenase (HFC, MMP-1) by P1′ modified t-butyl glycine analogues (**III**)*. Data obtained from Miller et al.[112] (Table 9).



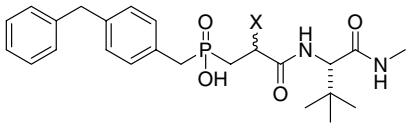
III

$$\log 1/IC_{50} = -0.47(\pm 0.08)\text{Clog}P + 8.51(\pm 0.44), \quad (3)$$

$n = 8$, $r^2 = 0.973$, $s = 0.200$, $q^2 = 0.939$, $Q = 4.930$, $F = 216.222$.

The negative Clog *P* term shows that for this data set hydrophilic molecules would present better inhibitory activity. This may be due to a shallower S1′ pocket as confirmed by X-ray crystal structures of HFC.[113]

*Inhibition of MMP-1 by phosphinic acid derivatives (**IV**)*. Data obtained from Reiter et al.[114] (Table 10).

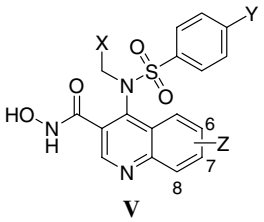


IV

$$\log 1/IC_{50} = -0.87(\pm 0.37)\text{Clog}P + 10.15(\pm 1.71), \quad (4)$$

$n = 8$, $r^2 = 0.848$, $s = 0.351$, $q_2 = 0.747$, $Q = 2.624$, $F = 33.474$.

*Inhibition of MMP-1 by quinoline derivatives (**V**)*. Data obtained from Zask et al.[115] (Table 11).



V

$$\log 1/IC_{50} = 1.61(\pm 0.71)\text{Clog}P - 0.32(\pm 0.12)\text{Clog}P^2 + 0.95(\pm 0.23)I_Y + 4.15(\pm 0.96), \quad (5)$$

$n = 20$, $r^2 = 0.891$, $s = 0.187$, $q^2 = 0.724$, $Q = 5.048$, $F = 43.596$, optimum Clog $P = 2.481$(2.170–2.663).

Parabolic dependence on Clog *P* provides an optimum hydrophobicity of 2.481. The indicator variable (I_Y) applies to those compounds, which have Y = OCH_3.

Table 9. Biological and physicochemical parameters used to derive QSAR equation 3 for the inhibition of human fibroblast collagenase (HFC, MMP-1) by P1′ modified *t*-butyl glycine analogues (**III**)

No.	X	Y	$\log 1/IC_{50}$ (Eq. 3)			Clog *P*
			Obsd.	Pred.	Δ	
1	$CH_2CH(Me)_2$	CONHOH	8.30	8.13	0.17	0.82
2[a]	C_8H_{17}	COOH	4.70	6.60	−1.90	4.10
3	$C_{13}H_{27}$	COOH	5.30	5.37	−0.07	6.74
4	$C_{15}H_{31}$	COOH	5.10	4.88	0.22	7.80
5	C_8H_{17}	CONHOH	7.00	7.08	−0.08	3.06
6	$C_{13}H_{27}$	CONHOH	5.52	5.85	−0.33	5.71
7	$C_{14}H_{29}$	CONHOH	5.52	5.61	−0.09	6.24
8	$C_{16}H_{33}$	CONHOH	5.30	5.12	0.18	7.29
9	$C_{14}H_{28}OH$	CONHOH	6.52	6.53	−0.01	4.25

[a] Not included in the derivation of QSAR 3.

Table 10. Biological and physicochemical parameters used to derive QSAR equation 4 for the inhibition of MMP-1 by phosphinic acid derivatives (**IV**)

No.	X	$\log 1/IC_{50}$ (Eq. 4)			Clog *P*
		Obsd.	Pred.	Δ	
1[a]	$CH_2CH(CH_3)_2$	7.22	6.41	0.81	4.30
2	$CH_2CH_2CH_3$	6.47	6.76	−0.29	3.90
3	$CH_2CH_2CF_3$	7.35	7.18	0.17	3.41
4	CH_2-cyclopropyl	6.70	6.83	−0.13	3.81
5	CH_2-cyclobutyl	6.75	6.35	0.40	4.37
6	$CH_2CH_2CH(CH_3)_2$	5.46	5.95	−0.49	4.83
7	$CH_2CH_2C_6H_5$	6.16	5.99	0.17	4.79
8	$CH_2C_6H_{11}$	5.74	5.37	0.37	5.49
9	$CH_2CH_2C_6H_{11}$	4.72	4.91	−0.19	6.02

[a] Not included in the derivation of QSAR 4.

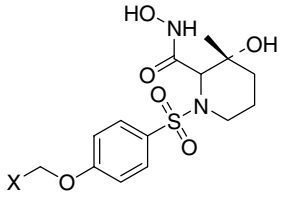
Table 11. Biological, physicochemical, and structural parameters used to derive QSAR equation 5 for the inhibition of MMP-1 by quinoline derivatives (**V**)

No.	X	Y	Z	log 1/IC$_{50}$ (Eq. 5)			Clog *P*	I_Y
				Obsd.	Pred.	*Δ*		
1	C_6H_5	OCH_3	6-Br	6.97	6.69	0.28	3.59	1
2	C_6H_5	OCH_3	7-Br	6.76	6.69	0.07	3.59	1
3	H	OCH_3	8-Br	6.65	6.95	−0.30	1.82	1
4	3-Pyridyl	OCH_3	8-Br	7.19	7.04	0.15	2.09	1
5	C_6H_5	OCH_3	6-CF_3	6.76	6.68	0.08	3.61	1
6	3-Pyridyl	OCH_3	7-CF_3	7.11	7.05	0.06	2.12	1
7	C_6H_5	OCH_3	7-CF_3	6.76	6.68	0.08	3.61	1
8[a]	C_6H_5	OCH_3	8-CF_3	6.03	6.68	−0.65	3.61	1
9	3-Pyridyl	OCH_3	8-I	7.12	7.09	0.03	2.35	1
10[a]	3-Pyridyl	OCH_3	8-OCH_3	7.34	6.75	0.59	1.46	1
11	3-Pyridyl	OCH_3	8-C_6H_5	6.82	6.98	−0.16	3.06	1
12	3-Pyridyl	OCH_3	8-(2-Thienyl)	6.87	7.03	−0.16	2.91	1
13	3-Pyridyl	OCH_3	8-$CH_2C_6H_5$	7.00	6.91	0.09	3.24	1
14	H	OCH_3	8-CH=CH_2	6.70	6.85	−0.15	1.62	1
15	C_6H_5	OCH_3	8-CH_3	6.82	6.94	−0.12	3.17	1
16	C_6H_5	OCH_3	8-CH_2CH_3	6.72	6.61	0.11	3.70	1
17	C_6H_5	OCH_3	8-$CH(CH_3)_2$	6.46	6.25	0.21	4.09	1
18	C_6H_5	OCH_3	8-$C(CH_3)_3$	5.51	5.78	−0.27	4.49	1
19	3-Pyridyl	C_6H_5	7-CF_3	5.38	5.54	−0.16	3.84	0
20	H	O-4-pyridyl	H	5.99	5.71	0.28	1.33	0
21	H	OCH_2CCCH_3	8-Br	6.02	6.07	−0.05	2.95	0
22	H	OCH_2CCCH_3	8-OCH_3	6.06	6.13	−0.07	2.31	0

[a] Not included in the derivation of QSAR 5.

The positive coefficient of the indicator variable indicates that the presence of methoxy group at Y-position will improve the activity.

*Inhibition of MMP-1 by 3-OH-3-methylpipecolic hydroxamates (**VI**)*. Data obtained from Noe et al.[116] (Table 12).



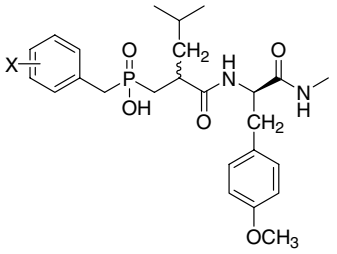
VI

$$\log 1/IC_{50} = 0.88(\pm 0.32)\text{Clog}P - 1.35(\pm 0.41)\text{CMR} + 0.82(\pm 0.55)I_X + 19.05(\pm 4.05), \quad (6)$$

$n = 16$, $r^2 = 0.846$, $s = 0.226$, $q^2 = 0.761$, $Q = 4.071$, $F = 21.974$, ClogP versus CMR: $r = 0.482$.

QSAR **6** reveals that hydrophobic and steric features influence the inhibitory activity in a linear model. Positive Clog *P* suggests that the inhibitory activity of the molecule increases with the increase of their hydrophobicity. On the contrary increases in the molar refractivity of the whole molecule (CMR) decrease the potency of the compounds (negative coefficient). The indicator variable (I_X) is for the presence of X = heterocyclic groups. The positive coefficient of the indicator variable indicates that the presence of heterocyclic groups at X-position will improve the activity.

*Inhibition of MMP-1 by phosphinic acid derivatives (**VII**)*. Data obtained from Reiter et al.[114] (Table 13).



VII

$$\log 1/IC_{50} = 0.21(\pm 0.08)\text{CMR}_{X\text{-}4} + 5.04(\pm 0.16), \quad (7)$$

$n = 9$, $r^2 = 0.850$, $s = 0.141$, $q^2 = 0.747$, $Q = 6.539$, $F = 39.667$, Clog *P* versus $\text{CMR}_{X\text{-}4}$: $r = 0.140$.

It seems that the molar refractivity of the substituent X-4 governs the inhibitory activity. The positive coefficient with $\text{CMR}_{X\text{-}4}$ suggests that in a rough way the larger the X-4 group, the higher the inhibitory activity. It is clear that bulk improves the activity. No role for a hydrophobic effect was found, which contradicts QSAR **4**. In this set the most active compound is an outlier. A more diverse set of compounds will be needed for further analysis.

Table 12. Biological, physicochemical, and structural parameters used to derive QSAR equation 6 for the inhibition of MMP-1 by 3-OH-3-methylpipecolic hydroxamates (**VI**)

No.	X	$\log 1/IC_{50}$ (Eq. 6)			Clog *P*	CMR	I_X
		Obsd.	Pred.	Δ			
1	2-Fluorophenyl	6.74	6.66	0.08	2.55	10.85	0
2	3-Fluorophenyl	6.47	6.66	−0.19	2.55	10.85	0
3	4-Fluorophenyl	6.38	6.66	−0.28	2.55	10.85	0
4	2-Chlorophenyl	6.57	6.52	0.05	3.12	11.33	0
5[a]	3-Chlorophenyl	6.07	6.52	−0.45	3.12	11.33	0
6	2-Methylphenyl	6.51	6.33	0.18	2.85	11.30	0
7	2-Methoxyphenyl	5.59	5.65	−0.06	2.32	11.45	0
8	2-Cyanophenyl	5.57	5.54	0.03	1.98	11.32	0
9[a]	2-Methyl-3-fluorophenyl	5.89	6.43	−0.54	3.00	11.32	0
10	2-Methyl-4-fluorophenyl	6.66	6.43	0.23	3.00	11.32	0
11	2-Methyl-5-fluorophenyl	6.22	6.43	−0.21	3.00	11.32	0
12	2-Chloro-4-fluorophenyl	6.51	6.63	−0.12	3.26	11.34	0
13	2-Fluoro-4-chlorophenyl	6.92	6.63	0.29	3.26	11.34	0
14	Pyridin-4-yl	6.72	6.34	0.38	0.91	10.63	1
15	Pyrazinyl	5.80	5.78	0.02	−0.05	10.42	1
16	4-Isoquinolinyl	5.11	5.10	0.01	2.08	12.31	1
17[a]	4-Quinolinyl	6.92	5.28	1.64	2.29	12.31	1
18	2-Chloro-4-pyridinyl	6.28	6.38	−0.10	1.70	11.12	1
19	2-Methyl-3-pyridinyl	5.80	6.11	−0.31	1.36	11.09	1

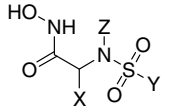
[a] Not included in the derivation of QSAR 6.

Table 13. Biological and physicochemical parameters used to derive QSAR equation 7 for the inhibition of MMP-1 by phosphinic acid derivatives (**VII**)

No.	X	$\log 1/IC_{50}$ (Eq. 7)			$CMR_{X\text{-}4}$
		Obsd.	Pred.	Δ	
1[a]	4-$CH_2C_6H_5$	6.57	5.68	0.89	2.98
2	H	4.82	5.05	−0.23	0
3	2-C_6H_5	4.96	5.05	−0.09	0
4	3-C_6H_5	5.29	5.05	0.24	0
5	4-C_6H_5	5.66	5.58	0.08	2.51
6	3-$CH_2CH_2C_6H_5$	5.13	5.05	0.08	0
7	4-$CH_2CH(Me)_2$	5.35	5.41	−0.06	1.72
8	4-$CH_2C_6H_{11}$	5.72	5.70	0.02	3.07
9	4-$SO_2C_6H_5$	5.77	5.77	0.00	3.38
10	4-OC_6H_5	5.55	5.61	−0.06	2.66

[a] Not included in the derivation of QSAR 7.

*Inhibition of MMP-1 by sulfonylated amino acid hydroxamates (**VIII**)*. Data obtained from Scozzafava and Supuran[117] (Table 14).



VIII

$$\log 1/K_i = 0.42(\pm 0.07)\mathrm{CMR} - 0.17(\pm 0.06)B5_X - 1.05(\pm 0.20)L_Y - 1.97(\pm 0.59)B1_Y + 15.24(\pm 1.79), \quad (8)$$

$n = 31$, $r^2 = 0.884$, $s = 0.177$, $q^2 = 0.838$, $Q = 5.311$, $F = 49.534$. Clog *P* versus CMR: $r = 0.858$; Clog *P* versus $B5_X$: $r = 0.609$; Clog *P* versus L_Y: $r = 0.200$. Clog *P* versus $B1_Y$: $r = 0.442$; CMR versus $B5_X$: $r = 0.265$; CMR versus L_Y: $r = 0.482$. CMR versus $B1_Y$: $r = 0.059$; $B5_X$ versus L_Y: $r = 0.035$; $B5_X$ versus $B1_Y$: $r = 0.062$. L_Y versus $B1_Y$: $r = 0.207$.

The most important term is the molar refractivity of the whole molecule (CMR), followed by sterimol parameters of X- and Y-substituents ($B5_X$, L_Y, and $B1_Y$). $B5_X$ is the sterimol parameter for the largest width of the X-substituent, while $B1_Y$ is for the smallest width of the Y-substituent, pointing to the steric effects at respective positions. L_Y is the sterimol parameter for the length of Y-substituent. With respect to QSAR **8**, it is important to note that there is a high mutual correlation between Clog *P* and CMR ($r = 0.858$). By considering Clog *P* in place of CMR, we can derive QSAR **8a**.

$$\log 1/K_i = 0.61(\pm 0.19)\mathrm{Clog}P - 0.35(\pm 0.14)B5_X - 0.28(\pm 0.27)L_Y - 3.37(\pm 1.17)B1_Y + 14.94(\pm 2.97), \quad (8a)$$

Table 14. Biological and physicochemical parameters used to derive QSAR equation 8 for the inhibition of MMP-1 by sulfonylated amino acid hydroxamates (**VIII**)

No.	X	Y	Z	log 1/K_i (Eq. 8)			CMR	$B5_X$	L_Y	$B1_Y$	Clog P
				Obsd.	Pred.	Δ					
1	H	C_6F_5	H	6.84	6.77	0.07	5.49	1.00	6.87	1.71	0.42
2	H	n-C_4F_9	$CH_2C_6H_5$	7.52	7.33	0.19	7.87	1.00	6.76	1.99	2.71
3	H	C_6F_5	$CH_2C_6H_5$	8.15	8.01	0.14	8.47	1.00	6.87	1.71	2.19
4	H	C_6H_4-4-OMe	$CH_2C_6H_5$	7.22	7.18	0.04	9.01	1.00	7.71	1.80	1.85
5	Me	C_6F_5	H	6.82	6.79	0.04	5.96	2.04	6.87	1.71	0.73
6	Me	n-C_4F_9	$CH_2C_6H_5$	7.59	7.35	0.24	8.34	2.04	6.76	1.99	3.02
7	Me	C_6F_5	$CH_2C_6H_5$	8.15	8.03	0.12	8.93	2.04	6.87	1.71	2.50
8	Me	C_6H_4-4-OMe	$CH_2C_6H_5$	7.24	7.19	0.04	9.47	2.04	7.71	1.80	2.16
9	$CHMe_2$	C_6F_5	H	6.86	6.98	−0.13	6.88	3.17	6.87	1.71	1.66
10	$CHMe_2$	n-C_4F_9	$CH_2C_6H_5$	7.68	7.54	0.14	9.26	3.17	6.76	1.99	3.95
11	$CHMe_2$	C_6F_5	$CH_2C_6H_5$	8.15	8.22	−0.07	9.86	3.17	6.87	1.71	3.43
12	$CHMe_2$	C_6H_4-4-OMe	$CH_2C_6H_5$	7.37	7.39	−0.02	10.40	3.17	7.71	1.80	3.09
13	CH_2CHMe_2	C_6F_5	H	6.81	6.96	−0.15	7.35	4.45	6.87	1.71	2.19
14	CH_2CHMe_2	n-C_4F_9	$CH_2C_6H_5$	7.80	7.52	0.28	9.73	4.45	6.76	1.99	4.48
15	CH_2CHMe_2	C_6F_5	$CH_2C_6H_5$	8.22	8.20	0.02	10.32	4.45	6.87	1.71	3.95
16	CH_2CHMe_2	C_6H_4-4-OMe	$CH_2C_6H_5$	7.36	7.36	−0.01	10.86	4.45	7.71	1.80	3.62
17	H	n-C_4F_9	$CH_2C_6H_4$-2-NO_2	7.60	7.59	0.02	8.49	1.00	6.76	1.99	2.37
18	H	C_6F_5	$CH_2C_6H_4$-2-NO_2	8.22	8.27	−0.05	9.08	1.00	6.87	1.71	1.85
19	H	C_6H_4-4-OMe	$CH_2C_6H_4$-2-NO_2	7.27	7.43	−0.17	9.62	1.00	7.71	1.80	1.52
20	H	n-C_4F_9	$CH_2C_6H_4$-4-NO_2	7.21	7.59	−0.38	8.49	1.00	6.76	1.99	2.45
21	H	C_6F_5	$CH_2C_6H_4$-4-NO_2	8.52	8.27	0.25	9.08	1.00	6.87	1.71	1.93
22	H	C_6H_4-4-OMe	$CH_2C_6H_4$-4-NO_2	7.55	7.43	0.12	9.62	1.00	7.71	1.80	1.60
23	Me	n-C_4F_9	$CH_2C_6H_4$-2-NO_2	7.62	7.60	0.02	8.95	2.04	6.76	1.99	2.68
24	Me	C_6F_5	$CH_2C_6H_4$-2-NO_2	8.16	8.29	−0.13	9.54	2.04	6.87	1.71	2.16
25	Me	C_6H_4-4-OMe	$CH_2C_6H_4$-2-NO_2	7.41	7.45	−0.04	10.08	2.04	7.71	1.80	1.82
26	Me	n-C_4F_9	$CH_2C_6H_4$-4-NO_2	7.22	7.60	−0.38	8.95	2.04	6.76	1.99	2.76
27	Me	C_6F_5	$CH_2C_6H_4$-4-NO_2	8.40	8.29	0.11	9.54	2.04	6.87	1.71	2.24
28	Me	C_6H_4-4-OMe	$CH_2C_6H_4$-4-NO_2	7.60	7.45	0.15	10.08	2.04	7.71	1.80	1.90
29	Me	n-C_4F_9	$CH_2C_6H_4$-2-Cl	7.43	7.55	−0.12	8.83	2.04	6.76	1.99	3.66
30	Me	C_6F_5	$CH_2C_6H_4$-2-Cl	8.00	8.24	−0.24	9.42	2.04	6.87	1.71	3.14
31	Me	C_6H_4-4-OMe	$CH_2C_6H_4$-2-Cl	7.28	7.40	−0.12	9.96	2.04	7.71	1.80	2.80

$n = 31$, $r^2 = 0.684$, $s = 0.292$, $q^2 = 0.556$, $Q = 2.832$, $F = 14.070$.

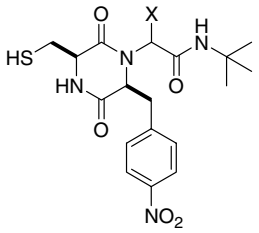
QSAR **8** was preferred because it is statistically better than QSAR **8a**. CMR is primarily a measure of bulk and of polarizability of the molecule. It seems that the bulk of the whole molecule plays a special role in increasing the inhibitory potency. CMR has the only positive term. One needs to minimize steric effects at X- and Y-positions while boosting CMR to achieve the greater activity. This is an interesting QSAR, since it is based on a large number of compounds and yields a good range in activity.

*Inhibition of MMP-1 by diketopiperazines (**IX**)*. Data obtained from Szardenings et al.[118] (Table 15).

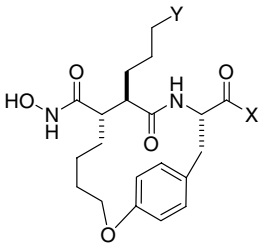
Table 15. Biological and physicochemical parameters used to derive QSAR equations Eqs. 9 and 34 for the inhibition of MMP-1 and MMP-9, respectively, by diketopiperazines (**IX**)

No.	X	log 1/IC_{50} (Eq. 9)			log 1/IC_{50} (Eq. 34)			CMR
		Obsd.	Pred.	Δ	Obsd.	Pred.	Δ	
1[a,b]	Cyclopropyl	7.43	7.82	−0.39	5.93	6.30	−0.37	11.96
2	$CH_2CH(Me)_2$	7.62	7.69	−0.07	6.24	6.15	0.09	12.56
3	$CH_2C_6H_5$	7.43	7.45	−0.02	5.92	5.87	0.05	13.68
4	C_7H_{15}	7.44	7.40	0.04	5.82	5.80	0.02	13.95
5[a]	C_6H_4-4-OCH_3	7.68	7.42	0.26	5.89	5.83	0.06	13.84
6	C_6H_4-4-OC_6H_5	6.97	6.99	−0.02	5.36	5.32	0.04	15.88
7	C_6H_4-4-OC_4H_9	7.14	7.13	0.01	5.49	5.48	0.01	15.23
8	C_6H_4-4-CH_2CH_3	7.39	7.36	0.03	5.59	5.76	−0.17	14.15
9	C_6H_4-4-C_6H_5	6.99	7.02	−0.03	5.37	5.36	0.01	15.73
10	C_6H_5	7.60	7.55	0.05	5.89	5.99	−0.10	13.22

[a] Not included in the derivation of QSAR 9.
[b] Not included in the derivation of QSAR 34.



IX



X

$$\log 1/IC_{50} = -0.21(\pm 0.04)CMR + 10.36(\pm 0.51), \quad (9)$$

$n = 8$, $r^2 = 0.973$, $s = 0.046$, $q^2 = 0.941$, $Q = 21.435$, $F = 216.222$.

The selectivity of these compounds is possibly due to the presence of an arginine at the bottom of S1′ pocket of collagenase-1. Most of the MMPs studied by X-ray crystallography have deep S1′ pockets, which allow the entry of large aliphatic or aromatic substituents. In collagenase-1, the pocket is blocked primarily by the side chain of an arginine residue, which is held rigidly in place by a network of hydrogen bonds.[113b,119,31] Authors assumed that the selectivity of nitrophenyl diketopiperazines (**IX**) may be due to the interaction of the aromatic NO_2 group with the arginine side chain.[118] But the mechanism of this interaction is not clear.

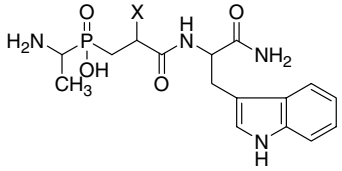
*Inhibition of MMP-1 by macrocyclic hydroxamic acids (**X**)*. Data obtained from Holms et al.[120] (Table 16).

$$\log 1/IC_{50} = -6.47(\pm 2.01)MgVol + 34.22(\pm 8.51), \quad (10)$$

$n = 8$, $r^2 = 0.912$, $s = 0.390$, $q^2 = 0.857$, $Q = 2.449$, $F = 62.182$. Clog P versus MgVol: $r = 0.441$.

MgVol is the McGowan's volume[105] and is a single important parameter for this data set. The negative coefficient of MgVol suggests a fitting to a macromolecule of limited steric capacity.

10.2.2.2. MMP-2 inhibitors. *Inhibition of MMP-2 by phosphinic pseudo-tripeptides (**XI**)*. Data obtained from Vassiliou et al.[121] (Table 17).



XI

Table 16. Biological and physicochemical parameters used to derive QSAR equation 10 for the inhibition of MMP-1 by macrocyclic hydroxamic acids (**X**)

No.	X	Y	$\log 1/IC_{50}$ (Eq. 10)			MgVol
			Obsd.	Pred.	Δ	
1	$NHCH_3$	4-Cl-C_6H_4	8.64	8.88	−0.24	3.92
2	$NHCH_3$	4-OCH_2CH_3-C_6H_4	8.17	7.47	0.70	4.13
3	$NHCH_3$	3,4-di-OCH_3-C_6H_3	6.64	7.09	−0.45	4.19
4	$NHCH_3$	2,5-di-OCH_3-C_6H_3	6.85	7.09	−0.24	4.19
5	$NHCH_3$	3,4,5-tri-OCH_3-C_6H_2	5.64	5.80	−0.16	4.39
6	$NHCH_3$	1-Naphthyl	7.55	7.28	0.27	4.16
7	C_6H_5	4-CH_3-C_6H_4	6.49	6.38	0.11	4.30
8	C_6H_5	3,5-di-Br-C_6H_3	5.04	5.03	0.01	4.51

Table 17. Biological and physicochemical parameters used to derive QSAR equations 11 and 47 for the inhibition of MMP-2 and MMP-14, respectively, by phosphinic pseudo-tripeptides (**XI**)

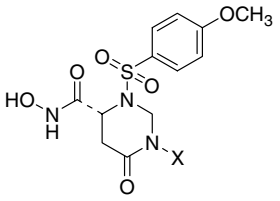
No.	X	$\log 1/K_i$ (Eq. 11)			$\log 1/K_i$ (Eq. 47)			Clog P	CMR
		Obsd.	Pred.	Δ	Obsd.	Pred.	Δ		
1	$CH_2C_6H_5$	6.60	6.57	0.03	5.69	5.67	0.02	1.24	12.61
2	$CH_2CH_2C_6H_5$	7.10	7.04	0.06	6.57	6.35	0.22	1.62	13.08
3	$CH_2CH_2CH_2C_6H_5$	7.51	7.70	−0.19	7.04	7.02	0.02	2.15	13.54
4	$CH_2OCH_2C_6H_5$	6.60	6.67	−0.07	6.26	6.57	−0.31	1.31	13.23
5	$CH_2SCH_2C_6H_5$	7.85	7.67	0.18	7.59	7.52	0.07	2.12	13.88

$$\log 1/K_i = 1.24(\pm 0.60)\mathrm{Clog}P + 5.04(\pm 1.03), \quad (11)$$

$n = 5$, $r^2 = 0.936$, $s = 0.162$, $q^2 = 0.781$, $Q = 5.969$, $F = 43.875$.

An interesting observation was made by the comparison of compounds **3**, **4**, and **5** illustrating the influence of a heteroatom in the γ position of the P1′ side chain. As compared to a carbon atom (compound **3**, Table 17), the presence of an oxygen in this position decreases the inhibitory potency (compound **4**, Table 17), while a sulfur significantly increases the potency of inhibition (compound **5**, Table 17).[121] This is also supported by our QSAR **11**, because the hydrophobicity of these three compounds is in the following order: compound **3** > compound **4** < compound **5** (Table 17).

*Inhibition of MMP-2 by 6-oxohexahydropyrimidines (**XII**).* Data obtained from Pikul et al.[122] (Table 18).



XII

$$\log 1/\mathrm{IC}_{50} = 0.58(\pm 0.32)\mathrm{Clog}P + 7.80(\pm 0.52), \quad (12)$$

$n = 6$, $r^2 = 0.865$, $s = 0.186$, $q^2 = 0.790$, $Q = 5.000$, $F = 25.630$.

*Inhibition of gelatinase (GelA, MMP-2) by P1′ modified phenylalanine analogues (**XIII**).* Data obtained from Miller et al.[112] (Table 19).

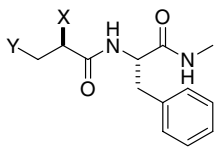
Table 18. Biological and physicochemical parameters used to derive QSAR equation 12 for the inhibition of MMP-2 by 6-oxohexahydropyrimidines (**XII**)

No.	X	$\log 1/\mathrm{IC}_{50}$ (Eq. 12)			Clog *P*
		Obsd.	Pred.	Δ	
1	CH_3	8.06	8.06	0.00	0.46
2	$CH(Me)_2$	8.28	8.55	−0.27	1.29
3	Cyclohexyl	9.15	9.19	−0.04	2.40
4	$C(Me)_3$	9.00	8.78	0.22	1.69
5	$CH_2C_6H_5$	9.00	9.03	−0.03	2.12
6	$CH_2CH_2OCH_3$	8.47	8.35	0.12	0.95

Table 19. Biological, physicochemical, and structural parameters used to derive QSAR equation 13 for the inhibition of MMP-2 by P1′ modified phenylalanine analogues (**XIII**)

No.	X	Y	$\log 1/\mathrm{IC}_{50}$ (Eq. 13)			Clog *P*	I_Y
			Obsd.	Pred.	Δ		
1	$CH_2CH(Me)_2$	CONHOH	8.40	7.92	0.48	0.91	0
2	$(CH_2)_3C_6H_5$	CONHOH	7.82	8.28	−0.46	1.93	0
3	C_6H_{13}	COOH	4.40	5.06	−0.66	3.13	1
4	C_7H_{15}	COOH	5.00	5.25	−0.25	3.66	1
5[a]	C_8H_{17}	COOH	6.70	5.43	1.27	4.19	1
6	C_9H_{19}	COOH	6.22	5.61	0.61	4.72	1
7	$C_{10}H_{21}$	COOH	6.00	5.80	0.20	5.25	1
8	$C_{12}H_{25}$	COOH	6.30	6.16	0.14	6.31	1
9	$C_{14}H_{29}$	COOH	6.70	6.53	0.17	7.36	1
10	$C_{15}H_{31}$	COOH	6.10	6.71	−0.61	7.89	1
11	$C_{16}H_{23}$	COOH	7.30	6.89	0.41	8.42	1
12	C_6H_{13}	CONHOH	8.00	8.34	−0.34	2.10	0
13	C_7H_{15}	CONHOH	9.00	8.52	0.48	2.62	0
14	C_8H_{17}	CONHOH	9.22	8.70	0.52	3.15	0
15	C_9H_{19}	CONHOH	9.00	8.88	0.12	3.68	0
16	$C_{10}H_{21}$	CONHOH	8.70	9.07	−0.37	4.21	0
17	$C_{12}H_{25}$	CONHOH	9.00	9.43	−0.43	5.27	0
18[a]	$C_{14}H_{29}$	CONHOH	7.52	9.80	−2.28	6.33	0
19[a]	$C_{16}H_{33}$	CONHOH	7.70	10.17	−2.47	7.39	0

[a] Not included in the derivation of QSAR 13.



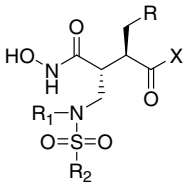
XIII

$$\log 1/IC_{50} = 0.35(\pm 0.16)\text{Clog}P - 3.63(\pm 0.68)I_Y + 7.61(\pm 0.60), \quad (13)$$

$n = 16$, $r^2 = 0.919$, $s = 0.471$, $q^2 = 0.869$, $Q = 2.036$, $F = 73.747$.

Positive Clog P suggests that highly hydrophobic P1′ modified phenylalanine analogues (**XIII**) would be more active. The indicator variable (I_Y) applies to those compounds, which have Y = COOH. The negative coefficient of the indicator variable indicates that the presence of CONHOH group at Y-position will improve the activity. As the large coefficient of indicator variable (I_Y) suggests that compounds with Y = COOH and CONHOH may act by different mechanism.

*Inhibition of MMP-2 by sulfonamide derivatives (**XIV**).* Data obtained from Martin et al.[123] (Table 20).



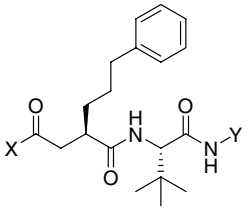
XIV

$$\log 1/IC_{50} = 0.43(\pm 0.12)\text{Clog}P - 0.43(\pm 0.32)I_R + 1.09(\pm 0.34)I_{R1} + 4.75(\pm 0.35), \quad (14)$$

$n = 20$, $r^2 = 0.893$, $s = 0.270$, $q^2 = 0.821$, $Q = 3.500$, $F = 44.511$.

QSAR **14** is an unusual equation. Despite rather wide variation in substituents at three positions, there is no outlier. Clog P is the most significant term, followed by two indicator variables (I_R) and (I_{R1}). The indicator variable (I_R) takes the value of 1 for the presence of the isopropyl group and 0 for cyclopentyl group in the R-position. Similarly, the indicator variable (I_{R1}) takes the value of 1 for the presence of the methyl group and 0 for others in R_1-position. The negative coefficient of I_R indicates that the presence of cyclopentyl group at R-position will improve the activity. The positive coefficient of I_{R1} indicates that CH_3 group is preferred over the other substituents at R_1-position.

*Inhibition of MMP-2 by succinyl hydroxamates and their carboxylic analogues (**XV**).* Data obtained from Fray et al.[124] (Table 21).



XV

Table 20. Biological, physicochemical, and structural parameters used to derive QSAR equations 14 and 20 for the inhibition of MMP-2 and MMP-3, respectively, by sulfonamide derivatives (**XIV**)

No.	R	X	R_1	R_2	log 1/IC_{50} (Eq. 14)			log 1/IC_{50} (Eq. 20)			Clog P	I_R	I_{R1}
					Obsd.	Pred.	Δ	Obsd.	Pred.	Δ			
1	Isopropyl	Piperidinyl	Methyl	Methyl	5.00	5.46	−0.46	5.40	5.77	−0.37	0.13	1	1
2	Isopropyl	Piperidinyl	Methyl	Ethyl	5.70	5.69	0.01	5.70	6.03	−0.33	0.65	1	1
3	Isopropyl	Piperidinyl	Methyl	Ph(4-OMe)	6.22	6.27	−0.05	6.40	6.70	−0.30	2.01	1	1
4	Isopropyl	Piperidinyl	Methyl	Dansyl	7.10	6.87	0.23	7.22	7.39	−0.17	3.41	1	1
5	Isopropyl	$N(Me)_2$	Methyl	Methyl	5.70	5.43	0.27	—	—	—	0.04	1	1
6	Cyclopentyl	Piperidinyl	Methyl	Methyl	6.05	6.16	−0.11	6.70	6.08	0.62	0.76	0	1
7	Cyclopentyl	Piperidinyl	Methyl	Ethyl	6.22	6.39	−0.17	6.40	6.34	0.05	1.29	0	1
8	Cyclopentyl	Piperidinyl	Methyl	Ph(4-OMe)	7.22	6.97	0.25	7.22	7.01	0.21	2.64	0	1
9	Cyclopentyl	Piperidinyl	Methyl	Dansyl	7.70	7.56	0.14	8.15	7.70	0.45	4.04	0	1
10	Cyclopentyl	Piperidinyl	Methyl	Naphthalyl	7.30	7.40	−0.10	7.30	7.51	−0.21	3.65	0	1
11	Cyclopentyl	Piperidinyl	*n*-Propyl	Methyl	5.52	5.53	−0.01	5.22	5.33	−0.11	1.82	0	0
12	Cyclopentyl	Piperidinyl	Cyclopentyl	Methyl	5.52	5.71	−0.19	5.00	5.54	−0.54	2.23	0	0
13	Cyclopentyl	Piperidinyl	Cyclopropyl	Methyl	5.70	5.23	0.47	5.70	4.98	0.72	1.11	0	0
14	Cyclopentyl	Piperidinyl	Isopropyl	Methyl	5.15	5.44	−0.29	5.16	5.22	−0.07	1.60	0	0
15	Cyclopentyl	Piperidinyl	Methyl	Isopropyl	6.40	6.52	−0.12	6.52	6.50	0.02	1.60	0	1
16	Cyclopentyl	Piperidinyl	Methyl	Ph(4-Cl)	7.00	7.20	−0.20	7.52	7.28	0.24	3.18	0	1
17	Cyclopentyl	Piperidinyl	Methyl	$N(Me)_2$	6.52	6.15	0.37	6.40	6.07	0.33	0.74	0	1
18	Cyclopentyl	Piperidinyl	Methyl	CF_3	6.30	6.64	−0.34	6.10	6.63	−0.53	1.87	0	1
19	Cyclopentyl	Morpholinyl	Methyl	Methyl	6.40	6.17	0.23	6.10	6.09	0.01	0.77	0	1
20	Cyclopentyl	Morpholinyl	Methyl	Ph(4-OMe)	7.02	6.97	0.05	7.00	7.02	−0.02	2.65	0	1

Table 21. Biological, physicochemical, and structural parameters used to derive QSAR equations 15 and 23 for the inhibition of MMP-2 and MMP-3, respectively, by succinyl hydroxamates and their carboxylic acid analogues (**XV**)

No.	X	Y	$\log 1/IC_{50}$ (Eq. 15)			$\log 1/IC_{50}$ (Eq. 23)			Clog P	I_X	I_Y
			Obsd.	Pred.	Δ	Obsd.	Pred.	Δ			
1[b]	NHOH	CH_3	9.47	9.74	−0.27	7.32	8.77	−1.45	1.84	1	0
2	NHOH	C_6H_5	9.00	8.74	0.26	7.89	7.79	0.10	3.69	1	0
3	NHOH	4-Pyridyl	9.70	9.10	0.60	8.36	8.14	0.22	3.02	1	0
4	NHOH	Cyclopentyl	8.80	8.95	−0.15	8.17	7.99	0.18	3.31	1	0
5	NHOH	Cyclohexyl	8.89	8.64	0.25	7.72	7.69	0.03	3.87	1	0
6	NHOH	$C(Me)_3$	8.24	9.07	−0.83	7.68	8.12	−0.44	3.07	1	0
7	NHOH	$CH(Me)C_6H_5$ [R]	9.42	8.56	0.86	8.05	7.61	0.44	4.03	1	0
8	NHOH	$CH(Me)C_6H_5$ [S]	7.21	7.18	0.03	7.40	7.61	−0.21	4.03	1	1
9	NHOH	$CH(CH_2CH_3)C_6H_5$ [R]	8.48	8.27	0.21	7.74	7.33	0.41	4.55	1	0
10	NHOH	$CH(CH_2CH_3)C_6H_5$ [S]	7.21	6.90	0.31	7.40	7.33	0.07	4.55	1	1
11	NHOH	$CH(CH_2OCH_3)C_6H_5$ [R]	7.82	8.67	−0.85	7.66	7.72	−0.06	3.81	1	0
12	NHOH	$CH(CH_2OCH_3)C_6H_5$ [S]	6.96	7.30	−0.34	7.60	7.72	−0.12	3.81	1	1
13	NHOH	$C(Me)_2C_6H_5$	8.47	8.34	0.13	7.14	7.40	−0.26	4.42	1	0
14[a]	NHOH	$CH(C_6H_5)_2$	6.38	7.99	−1.61	7.32	7.06	0.26	5.06	1	0
15	NHOH	$C(Me)(C_6H_5)_2$	7.59	7.78	−0.19	6.24	6.85	−0.61	5.46	1	0
16	OH	CH_3	7.96	8.14	−0.18	6.39	6.70	−0.31	2.87	0	0
17	OH	C_6H_5	7.52	7.13	0.39	6.32	5.71	0.61	4.73	0	0
18	OH	4-Pyridyl	8.19	7.49	0.70	6.56	6.07	0.49	4.06	0	0
19	OH	Cyclopentyl	7.27	7.34	−0.07	5.47	5.92	−0.45	4.34	0	0
20	OH	Cyclohexyl	7.42	7.03	0.39	6.25	5.62	0.63	4.90	0	0
21[b]	OH	$C(Me)_3$	7.08	7.47	−0.39	5.00	6.04	−1.04	4.11	0	0
22	OH	$CH(Me)C_6H_5$ [R]	7.30	6.95	0.35	5.55	5.54	0.01	5.06	0	0
23	OH	$CH(Me)C_6H_5$ [S]	5.80	5.57	0.23	5.27	5.54	−0.27	5.06	0	1
24	OH	$CH(CH_2CH_3)C_6H_5$ [R]	6.48	6.66	−0.18	5.30	5.25	0.05	5.59	0	0
25	OH	$CH(CH_2CH_3)C_6H_5$ [S]	5.29	5.29	0.00	5.21	5.25	−0.04	5.59	0	1
26[a]	OH	$CH(CH_2OCH_3)C_6H_5$ [R]	5.21	7.06	−1.85	5.07	5.65	−0.58	4.85	0	0
27	OH	$CH(CH_2OCH_3)C_6H_5$ [S]	5.46	5.69	−0.23	5.49	5.65	−0.16	4.85	0	1
28	OH	$C(Me)_2C_6H_5$	6.55	6.73	−0.18	—	—	—	5.46	0	0
29[b]	OH	$CH(C_6H_5)_2$	5.61	6.39	−0.78	6.20	4.98	1.22	6.10	0	0
30	OH	$C(Me)(C_6H_5)_2$	6.11	6.17	−0.06	—	—	—	6.50	0	0

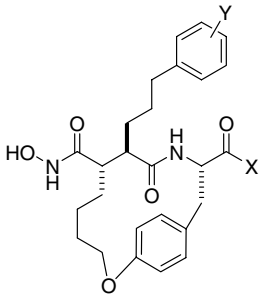
[a] Not included in the derivation of QSAR 15.
[b] Not included in the derivation of QSAR 23.

$$\log 1/IC_{50} = -0.54(\pm 0.21)\text{Clog}P + 1.05(\pm 0.42)I_X - 1.37(\pm 0.44)I_Y + 9.69(\pm 1.05), \quad (15)$$

$n = 28$, $r^2 = 0.881$, $s = 0.453$, $q^2 = 0.847$, $Q = 2.073$, $F = 59.227$.

Indicator variable $I_X = 1$ for the presence of X = NHOH and 0 for X = OH. Similarly, $I_Y = 1$ for the presence of Y = *S*-isomers and 0 for others. The positive coefficient of the indicator variable (I_X) indicates that the presence of NHOH group at X-position will improve the activity. The presence of Y = *S*-isomer decreases the activity as evidenced by the negative coefficient of indicator variable (I_Y). Thus, QSAR **15** supports the author's finding, that is, the inhibitory activity of succinyl hydroxamates and their carboxylic acid analogues (**XV**) against MMP-2 is dependent on P3′ group chirality.[124]

*Inhibition of MMP-2 by macrocyclic hydroxamic acids (**XVI**).* Data obtained from Holms et al.[120] (Table 22).



XVI

$$\log 1/IC_{50} = -1.13(\pm 0.35)\text{CMR} + 24.94(\pm 5.43), \quad (16)$$

$n = 11$, $r^2 = 0.858$, $s = 0.548$, $q^2 = 0.799$, $Q = 1.690$, $F = 54.380$.

CMR refers to the overall calculated molar refractivity. Since MR is primarily a measure of bulk, a negative coefficient suggests steric hindrance. There is not a significant correlation between Clog P and CMR ($r = 0.630$). Substituting Clog P for CMR in Eq. 16 gives a very poor fit ($r^2 = 0.167$, $q^2 = -0.139$). Thus, CMR cannot be replaced by Clog P for this data set.

Table 22. Biological and physicochemical parameters used to derive QSAR equation 16 for the inhibition of MMP-2 by macrocyclic hydroxamic acids (**XVI**)

No.	X	Y	$\log 1/IC_{50}$ (Eq. 16)			CMR
			Obsd.	Pred.	Δ	
1	$NHCH_3$	4-Cl	9.59	9.14	0.45	13.99
2	$NHCH_3$	4-OCH_2CH_3	9.10	8.47	0.63	14.58
3	$NHCH_3$	3,4-di-OCH_3	8.00	8.30	−0.30	14.73
4	$NHCH_3$	2,5-di-OCH_3	7.89	8.30	−0.41	14.73
5	$NHCH_3$	3,4,5-tri-OCH_3	6.96	7.60	−0.64	15.35
6[a]	$NHCH_3$	3,5-di-CF_3	5.66	8.54	−2.88	14.52
7	$NHCH_3$	3-CH_3, 5-$CH(CH_3)_2$	7.02	7.60	−0.58	15.35
8	C_6H_5	4-CH_3	7.96	7.27	0.69	15.64
9	C_6H_5	3,4,5-tri-OCH_3	5.47	5.71	−0.24	17.03
10	C_6H_5	3,5-di-OCH_3	6.00	6.40	−0.40	16.41
11	C_6H_5	3,5-di-Br	6.64	6.04	0.60	16.73
12	C_6H_5	3-$OCH_2CH_2OCH_3$, 4-OCH_3	5.40	5.18	0.22	17.49

[a] Not included in the derivation of QSAR 16.

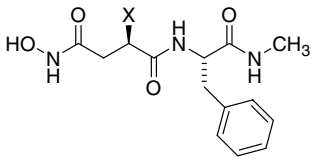
*Inhibition of MMP-2 by sulfonylated amino acid hydroxamates (**VIII**)*. Data obtained from Scozzafava and Supuran[117] (Table 23).

$$\log 1/K_i = 0.41(\pm 0.05)\text{CMR} - 0.18(\pm 0.08)L_X - 1.17(\pm 0.19)L_Y + 13.51(\pm 1.29), \quad (17)$$

$n = 39$, $r^2 = 0.908$, $s = 0.233$, $q^2 = 0.884$, $Q = 4.090$, $F = 115.145$. Clog P versus CMR: $r = 0.613$; Clog P versus L_X: $r = 0.469$; Clog P versus L_Y: $r = 0.366$. CMR versus L_X: $r = 0.134$; CMR versus L_Y: $r = 0.269$.

The most important term is the molar refractivity of the whole molecule (CMR), followed by sterimol parameters for the length of X and Y substituents (L_X and L_Y).

10.2.2.3. MMP-3 inhibitors. *Inhibition of MMP-3 by P1′ hydroxamate derivatives (**XVII**)*. Data obtained from Gowravaram et al.[125] (Table 24).

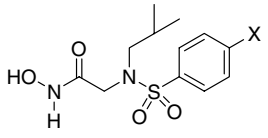


XVII

$$\log 1/K_i = 0.58(\pm 0.14)\text{Clog}P + 6.57(\pm 0.20), \quad (18)$$

$n = 11$, $r^2 = 0.904$, $s = 0.245$, $q^2 = 0.848$, $Q = 3.882$, $F = 84.750$.

*Inhibition of recombinant human stromelysin (SLN; MMP-3) by hydroxamic acids having modifications of the aryl substituent (**XVIII**)*. Data obtained from MacPherson et al.[126] (Table 25).



XVIII

$$\log 1/K_i = 0.64(\pm 0.19)\text{Clog}P + 4.64(\pm 0.50), \quad (19)$$

$n = 12$, $r^2 = 0.857$, $s = 0.313$, $q^2 = 0.806$, $Q = 2.958$, $F = 59.930$.

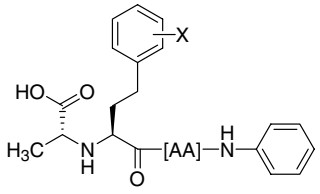
*Inhibition of MMP-3 by sulfonamide derivatives (**XIV**)*. Data obtained from Martin et al.[123] (Table 20).

$$\log 1/IC_{50} = 0.50(\pm 0.17)\text{Clog}P + 1.27(\pm 0.46)I_{R1} + 4.43(\pm 0.50), \quad (20)$$

$n = 19$, $r^2 = 0.836$, $s = 0.380$, $q^2 = 0.745$, $Q = 2.405$, $F = 40.780$.

The indicator variable (I_{R1}) takes the value of 1 for the presence of CH_3 group and 0 for others in R_1 position.

*Inhibition of human stromelysin-1 (MMP-3) by N-carboxyalkyl dipeptides containing substituted P1′ homophenylalanines (**XIX**)*. Data obtained from Sahoo et al.[127] (Table 26).



XIX

$$\log 1/K_i = 0.53(\pm 0.15)\text{Clog}P - 1.17(\pm 0.41)I - 0.64(\pm 0.16)L_{X\text{-}3} + 7.13(\pm 0.50), \quad (21)$$

$n = 18$, $r^2 = 0.893$, $s = 0.241$, $q^2 = 0.834$, $Q = 3.921$, $F = 38.947$.

NMR and X-ray crystal structure studies of the inhibited catalytic domain of the enzyme show that S1′ subsite is a deep hydrophobic pocket.[128] This may lead one to assume that P1′ substituents might interact with a deep hydrophobic pocket of the S1′ subsite. $L_{X\text{-}3}$ represents the sterimol parameter for the length of substituents at third position of the phenyl ring. Negative coefficient

Table 23. Biological and physicochemical parameters used to derive QSAR equations 17 and 33 for the inhibition of MMP-2 and MMP-9, respectively, by sulfonylated amino acid hydroxamates (**VIII**)

No.	X	Y	Z	$\log 1/K_i$ (Eq. 17)			$\log 1/K_i$ (Eq. 33)			Clog *P*	CMR	L_X	L_Y
				Obsd.	Pred.	Δ	Obsd.	Pred.	Δ				
1	H	*n*-C_4F_9	H	7.12	7.25	−0.13	6.90	6.92	−0.02	1.28	4.90	2.06	6.76
2	H	C_6F_5	H	7.36	7.36	0.00	7.00	7.38	−0.38	0.42	5.49	2.06	6.87
3	H	C_6H_4-4-OMe	H	6.96	6.60	0.36	6.84	6.39	0.45	−0.27	6.03	2.06	7.71
4	H	*n*-C_4F_9	$CH_2C_6H_5$	8.41	8.47	−0.06	8.30	8.10	0.20	2.71	7.87	2.06	6.76
5	H	C_6F_5	$CH_2C_6H_5$	8.82	8.58	0.24	8.92	8.43	0.49	2.19	8.47	2.06	6.87
6	H	C_6H_4-4-OMe	$CH_2C_6H_5$	7.74	7.82	−0.08	7.38	7.31	0.07	1.85	9.01	2.06	7.71
7	Me	*n*-C_4F_9	H	7.16	7.29	−0.13	6.92	7.07	−0.15	1.59	5.36	2.87	6.76
8	Me	C_6F_5	H	7.40	7.41	−0.01	7.02	7.53	−0.51	0.73	5.96	2.87	6.87
9	Me	C_6H_4-4-OMe	H	7.06	6.65	0.41	6.86	6.54	0.32	0.04	6.50	2.87	7.71
10	Me	*n*-C_4F_9	$CH_2C_6H_5$	8.49	8.51	−0.02	8.37	8.25	0.12	3.02	8.34	2.87	6.76
11	Me	C_6F_5	$CH_2C_6H_5$	9.05	8.63	0.42	8.85	8.59	0.26	2.50	8.93	2.87	6.87
12	Me	C_6H_4-4-OMe	$CH_2C_6H_5$	7.82	7.86	−0.04	7.46	7.47	−0.01	2.16	9.47	2.87	7.71
13	$CHMe_2$	*n*-C_4F_9	H	7.18	7.45	−0.27	6.92	7.26	−0.34	2.52	6.29	4.11	6.76
14[a]	$CHMe_2$	C_6F_5	H	7.39	7.56	−0.17	7.05	7.72	−0.67	1.66	6.88	4.11	6.87
15	$CHMe_2$	C_6H_4-4-OMe	H	7.09	6.80	0.29	6.90	6.73	0.17	0.97	7.42	4.11	7.71
16	$CHMe_2$	*n*-C_4F_9	$CH_2C_6H_5$	8.62	8.67	−0.05	8.37	8.44	−0.07	3.95	9.26	4.11	6.76
17	$CHMe_2$	C_6F_5	$CH_2C_6H_5$	9.10	8.78	0.32	8.92	8.77	0.15	3.43	9.86	4.11	6.87
18	$CHMe_2$	C_6H_4-4-OMe	$CH_2C_6H_5$	7.96	8.02	−0.06	7.57	7.65	−0.08	3.09	10.40	4.11	7.71
19	CH_2CHMe_2	*n*-C_4F_9	H	7.21	7.49	−0.28	7.44	7.33	0.11	3.05	6.75	4.92	6.76
20[a]	CH_2CHMe_2	C_6F_5	H	7.41	7.61	−0.20	6.91	7.79	−0.88	2.19	7.35	4.92	6.87
21	CH_2CHMe_2	C_6H_4-4-OMe	H	7.08	6.85	0.23	7.11	6.80	0.31	1.50	7.89	4.92	7.71
22	CH_2CHMe_2	*n*-C_4F_9	$CH_2C_6H_5$	8.72	8.71	0.01	8.40	8.51	−0.11	4.48	9.73	4.92	6.76
23	CH_2CHMe_2	C_6F_5	$CH_2C_6H_5$	9.10	8.83	0.27	8.96	8.85	0.11	3.95	10.32	4.92	6.87
24[a]	CH_2CHMe_2	C_6H_4-4-OMe	$CH_2C_6H_5$	8.00	8.07	−0.07	8.89	7.73	1.16	3.62	10.86	4.92	7.71
25	H	*n*-C_4F_9	$CH_2C_6H_4$-2-NO_2	8.43	8.72	−0.29	8.34	8.58	−0.24	2.37	8.49	2.06	6.76
26	H	C_6F_5	$CH_2C_6H_4$-2-NO_2	8.85	8.83	0.02	8.89	8.91	−0.02	1.85	9.08	2.06	6.87
27	H	C_6H_4-4-OMe	$CH_2C_6H_4$-2-NO_2	7.82	8.07	−0.25	7.41	7.79	−0.38	1.52	9.62	2.06	7.71
28	H	*n*-C_4F_9	$CH_2C_6H_4$-4-NO_2	8.82	8.72	0.10	8.70	8.55	0.15	2.45	8.49	2.06	6.76
29	H	C_6F_5	$CH_2C_6H_4$-4-NO_2	9.16	8.83	0.33	9.22	8.88	0.34	1.93	9.08	2.06	6.87
30	H	C_6H_4-4-OMe	$CH_2C_6H_4$-4-NO_2	7.75	8.07	−0.33	7.51	7.76	−0.25	1.60	9.62	2.06	7.71
31	Me	*n*-C_4F_9	$CH_2C_6H_4$-2-NO_2	8.54	8.76	−0.22	8.36	8.73	−0.37	2.68	8.95	2.87	6.76
32	Me	C_6F_5	$CH_2C_6H_4$-2-NO_2	9.10	8.88	0.22	9.00	9.06	−0.06	2.16	9.54	2.87	6.87
33	Me	C_6H_4-4-OMe	$CH_2C_6H_4$-2-NO_2	7.89	8.11	−0.22	7.62	7.94	−0.32	1.82	10.08	2.87	7.71
34	Me	*n*-C_4F_9	$CH_2C_6H_4$-4-NO_2	8.85	8.76	0.09	8.82	8.70	0.12	2.76	8.95	2.87	6.76
35	Me	C_6F_5	$CH_2C_6H_4$-4-NO_2	9.16	8.88	0.28	9.22	9.03	0.19	2.24	9.54	2.87	6.87
36	Me	C_6H_4-4-OMe	$CH_2C_6H_4$-4-NO_2	7.82	8.11	−0.29	7.55	7.91	−0.36	1.90	10.08	2.87	7.71
37	Me	*n*-C_4F_9	$CH_2C_6H_4$-2-Cl	8.43	8.71	−0.28	8.30	8.30	0.00	3.66	8.83	2.87	6.76
38	Me	C_6F_5	$CH_2C_6H_4$-2-Cl	8.82	8.83	−0.01	8.77	8.63	0.14	3.14	9.42	2.87	6.87
39	Me	C_6H_4-4-OMe	$CH_2C_6H_4$-2-Cl	7.92	8.07	−0.15	7.51	7.51	0.00	2.80	9.96	2.87	7.71

[a] Not included in the derivation of QSAR 33.

Table 24. Biological and physicochemical parameters used to derive QSAR equation 18 for the inhibition of MMP-3 by P1′ hydroxamate derivatives (**XVII**)

No.	X	$\log 1/K_i$ (Eq. 18)			Clog *P*
		Obsd.	Pred.	Δ	
1	CH_2CHMe_2	7.10	7.09	0.01	0.91
2	$(CH_2)_4OH$	5.66	6.02	−0.36	−0.95
3	$(CH_2)_5OH$	6.37	6.33	0.04	−0.42
4	$(CH_2)_3CONHC_3H_7$	6.44	6.14	0.30	−0.73
5	$(CH_2)_3CONHCH_2C_6H_5$	7.04	6.71	0.33	0.24
6[a]	$(CH_2)_3CONH(CH_2)_2C_6H_5$	8.22	6.75	1.47	0.30
7	$(CH_2)_4NHCO(CH_2)_2CH_3$	6.15	6.45	−0.30	−0.21
8	$(CH_2)_3OCH_2C_6H_5$	7.37	7.27	0.10	1.21
9	$(CH_2)_4OCH_2C_6H_5$	7.82	7.57	0.25	1.73
10	$(CH_2)_5OCH_2C_6H_5$	7.72	7.88	−0.16	2.26
11	$(CH_2)_4OC_6H_5$	7.55	7.65	−0.10	1.88
12	$(CH_2)_5OC_6H_5$	7.85	7.96	−0.11	2.40

[a] Not included in the derivation of QSAR 18.

Table 25. Biological and physicochemical parameters used to derive QSAR equation 19 for the inhibition of MMP-3 by hydroxamic acids having modifications of the aryl substituent (**XVIII**)

No.	X	$\log 1/K_i$ (Eq. 19)			Clog *P*
		Obsd.	Pred.	*Δ*	
1[a]	OCH_3	6.88	5.68	1.20	1.61
2	Cl	6.03	6.03	0.00	2.15
3	H	5.75	5.57	0.18	1.44
4	CH_3	5.49	5.89	−0.40	1.94
5	F	5.49	5.66	−0.17	1.58
6	$N(CH_3)_2$	5.36	5.87	−0.51	1.91
7	NH_2	5.30	5.10	0.20	0.71
8[a]	CF_3	5.27	6.14	−0.87	2.32
9	$O(CH_2)_3CH_3$	7.24	6.70	0.54	3.19
10	$OCH_2CH_2CH(CH_3)_2$	7.11	6.95	0.16	3.59
11	$O(CH_2)_5CH_3$	7.20	7.38	−0.18	4.25
12	$OCH_2C_6H_{11}$	7.22	7.38	−0.16	4.26
13	$OCH(CH_3)_2$	6.47	6.22	0.25	2.44
14	$OCH_2CH_2OC_2H_5$	5.95	5.86	0.09	1.88

[a] Not included in the derivation of QSAR 19.

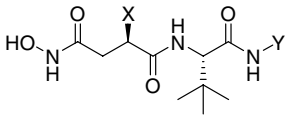
Table 26. Biological, physicochemical, and structural parameters used to derive QSAR equation 21 for the inhibition of human stromelysin-1 (MMP-3) by *N*-carboxyalkyl dipeptides containing substituted P1′ homophenylalanines (**XIX**)

No.	X	AA	$\log 1/K_i$ (Eq. 21)			Clog *P*	*I*	$L_{X\text{-}3}$
			Obsd.	Pred.	*Δ*			
1	H	L-Leucine	6.33	6.56	−0.23	3.62	1	2.06
2	2-OH	L-Leucine	5.80	6.18	−0.38	2.90	1	2.06
3[a]	3-OH	L-Leucine	6.64	5.77	0.87	2.95	1	2.74
4	4-OH	L-Leucine	6.48	6.21	0.27	2.95	1	2.06
5	$3\text{-}OCH_3$	L-Leucine	5.33	5.29	0.04	3.54	1	3.98
6	3-Cl	L-Leucine	5.75	6.01	−0.26	4.33	1	3.52
7	4-Cl	L-Leucine	6.72	6.94	−0.22	4.33	1	2.06
8	4-F	L-Leucine	6.72	6.64	0.08	3.76	1	2.06
9[a]	$4\text{-}CF_3$	L-Leucine	6.08	7.03	−0.95	4.50	1	2.06
10	$3\text{-}CH_3$	L-Leucine	6.66	6.31	0.35	4.12	1	2.87
11	$4\text{-}CH_3$	L-Leucine	6.96	6.83	0.13	4.12	1	2.06
12	$3,4\text{-di-}CH_3$	L-Leucine	6.66	6.55	0.11	4.57	1	2.87
13	$4\text{-}CH_2CH_3$	L-Leucine	7.14	7.11	0.03	4.65	1	2.06
14	$4\text{-}CH_2CH_2CH_3$	L-Leucine	7.74	7.39	0.35	5.18	1	2.06
15[a]	4-CH(Me)2	L-Leucine	6.75	7.32	−0.57	5.05	1	2.06
16	$3\text{-}CH_2CH(Me)_2$	L-Leucine	5.75	5.77	−0.02	5.58	1	4.92
17	$4\text{-}CH_2CH(Me)_2$	L-Leucine	7.37	7.60	−0.23	5.58	1	2.06
18	H	L-Arginine	6.64	6.51	0.13	1.33	0	2.06
19	$4\text{-}CH_2CH_2CH_3$	L-Arginine	7.48	7.34	0.14	2.88	0	2.06
20	$4\text{-}(CH_2)_3CH_3$	L-Arginine	7.44	7.62	−0.18	3.41	0	2.06
21	$4\text{-}OC_2H_5$	L-Arginine	6.66	6.75	−0.09	1.77	0	2.06

[a] Not included in the derivation of QSAR 21.

with $L_{X\text{-}3}$ suggests unfavorable steric effect. The indicator variable *I* takes the value of 1 for the presence of L-leucine and 0 for L-arginine. The negative coefficient of *I* shows that the later is considerably more effective.

*Inhibition of MMP-3 by succinyl hydroxamic acids (**XX**)*. Data obtained from Fray and Dickinson[129] (Table 27).



XX

$$\log 1/IC_{50} = 30.54(\pm 7.06)C\pi_X - 3.09(\pm 0.70)C\pi_X^2 - 0.49(\pm 0.21)C\pi_Y - 65.94(\pm 17.53), \quad (22)$$

$n = 15$, $r^2 = 0.906$, $s = 0.296$, $q^2 = 0.842$, $Q = 3.216$, $F = 35.340$. optimum $C\pi_X = 4.936(4.866–4.998)$.

X- and Y-substituents refer to P1′ and P3′ groups, respectively. The parabolic correlation with $C\pi_X$ (calculated hydrophobicity of X-substituents) suggests hydrophobic interactions with S1′ site but limited to the optimum value of $C\pi_X = 4.94$. That is, increase in the hydrophobicity leads to increase in the inhibitory potency up to an optimum value of 4.94 and then activity decreases. The negative coefficient of $C\pi_Y$ indicates that increase in hydrophobicity of Y-substituents may

Table 27. Biological and physicochemical parameters used to derive QSAR equation 22 for the inhibition of MMP-3 by succinyl hydroxamic acids (**XX**)

No.	X	Y	log 1/IC$_{50}$ (Eq. 22)			Cπ_X	Cπ_Y
			Obsd.	Pred.	Δ		
1	$(CH_2)_8CH_3$	CH(Me)C$_6$H$_5$(R)	7.60	8.22	−0.62	4.77	2.29
2	$CH_2CH_2C_6H_4$-4-(4-F-C$_6$H$_4$)	CH(Me)C$_6$H$_5$(R)	7.59	7.76	−0.18	4.51	2.29
3	$CH_2CH_2CH_2C_6H_{11}$	CH(Me)C$_6$H$_5$(R)	6.92	6.83	0.09	4.24	2.29
4	$CH_2CH_2CH_2C_6H_4$-4-C$_6$H$_5$	CH(Me)C$_6$H$_5$(R)	8.59	8.31	0.28	4.90	2.29
5	$CH_2CH_2CH_2C_6H_4$-4-C$_6$H$_5$	CH(C$_6$H$_5$)$_2$	8.06	7.80	0.26	4.90	3.33
6	$CH_2CH_2CH_2C_6H_3$-3-F-4-C$_6$H$_5$	CH(Me)C$_6$H$_5$(R)	8.14	8.28	−0.13	5.04	2.29
7	$CH_2CH_2CH_2$-C$_6$H$_3$-3-F-4-C$_6$H$_5$	CH(C$_6$H$_5$)$_2$	8.00	7.77	0.23	5.04	3.33
8	$CH_2CH_2CH_2$-2-fluorene	CH(Me)C$_6$H$_5$(R)	8.42	8.31	0.11	4.95	2.29
9	$CH_2CH_2CH_2$-C$_6$H$_3$-3-Cl-4-C$_6$H$_5$	CH(Me)C$_6$H$_5$(R)	7.89	7.75	0.14	5.36	2.29
10	$CH_2CH_2CH_2$-C$_6$H$_3$-3-CH$_3$-4-C$_6$H$_5$	CH(Me)C$_6$H$_5$(R)	8.23	8.23	0.00	5.10	2.29
11	$CH_2CH_2CH_2$-C$_6$H$_3$-3-CH_2CH_3-4-C$_6$H$_5$	CH(Me)C$_6$H$_5$(R)	6.35	6.83	−0.48	5.63	2.29
12	$CH_2CH_2CH_2$-C$_6$H$_3$-3-OCH$_3$-4-C$_6$H$_5$	CH(Me)C$_6$H$_5$(R)	6.96	6.89	0.07	4.26	2.29
13	$CH_2CH_2CH_2$-C$_6$H$_3$-3-CF$_3$-4-C$_6$H$_5$	CH(Me)C$_6$H$_5$(R)	6.11	6.09	0.02	5.78	2.29
14	$CH_2CH_2CH_2$-C$_6$H$_3$-3-CH$_3$-4-C$_6$H$_5$	CH_3	9.30	9.30	0.00	5.10	0.10
15	$CH_2CH_2CH_2$-C$_6$H$_3$-3-CF$_3$-4-C$_6$H$_5$	CH_3	7.40	7.17	0.23	5.78	0.10

decrease the inhibitory potency. Thus, S3′ pocket may be hydrophilic in nature.

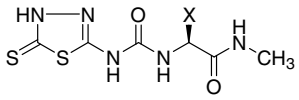
*Inhibition of MMP-3 by succinyl hydroxamates and their carboxylic analogues (**XV**)*. Data obtained from Fray et al.[124] (Table 21).

$$\log 1/IC_{50} = -0.53(\pm 0.22)\text{Clog}P + 1.52(\pm 0.34)I_X + 8.22(\pm 1.05), \quad (23)$$

$n = 25$, $r^2 = 0.895$, $s = 0.366$, $q^2 = 0.860$, $Q = 2.585$, $F = 93.762$.

QSAR **23** is very similar to QSAR **15**. The negative Clog *P* term shows that the hydrophilic molecules would present better inhibitory activity. Indicator variable $I_X = 1$ for the presence of X = NHOH and 0 for X = OH. The positive coefficient of the indicator variable (I_X) indicates that the presence of NHOH group at X-position will improve the activity as observed in QSAR **15**.

*Inhibition of stromelysin-1 (MMP-3) by thiadiazole urea methylamides (**XXI**)*. Data obtained from Jacobsen et al.[130] (Table 28).

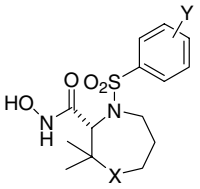


XXI

$$\log 1/K_i = 0.53(\pm 0.23)\text{CMR} + 1.98(\pm 0.68), \quad (24)$$

$n = 8$, $r^2 = 0.836$, $s = 0.324$, $q^2 = 0.718$, $Q = 2.824$, $F = 30.585$.

*Inhibition of MMP-3 by thiazepine derivatives (**XXII**)*. Data obtained from Almstead et al.[131] (Table 29).



XXII

$$\log 1/IC_{50} = -1.48(\pm 0.53)\sigma^+ + 7.12(\pm 0.30), \quad (25)$$

$n = 9$, $r^2 = 0.860$, $s = 0.212$, $q^2 = 0.759$, $Q = 4.373$, $F = 43.000$.

This is an interesting equation, which correlates with σ^+ term of Y-substituents. Negative coefficient of σ^+ indicates that electron-donating Y-group may enhance the inhibitory potency of the molecules. Almstead et al.[131] proposed a catalytic site for MMP-3 with the help of compound **1** (Table 29) and suggested that the methoxyphenylsulfonamide group is directed toward S1′ site and

Table 28. Biological and physicochemical parameters used to derive QSAR equation 24 for the inhibition of stromelysin-1 (MMP-3) by thiadiazole urea methylamides (**XXI**)

No.	X	log 1/K_i (Eq. 24)			CMR
		Obsd.	Pred.	Δ	
1	H	3.78	3.95	−0.17	6.18
2	$CH_2C_6H_5$	6.15	5.53	0.62	9.15
3	*ent*-$CH_2C_6H_5$	5.28	5.53	−0.25	9.15
4	CH_2-cyclohexane	5.39	5.58	−0.19	9.25
5	$CH_2CH(CH_3)_2$	4.77	4.94	−0.17	8.03
6	C_6H_5	5.39	5.28	0.11	8.69
7	CH_2OH	4.51	4.28	0.23	6.79
8	$CH_2OCH_2C_6H_5$	5.70	5.86	−0.16	9.77

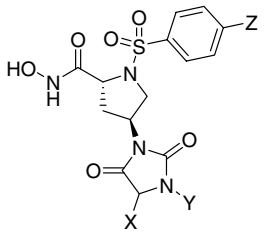
Table 29. Biological and physicochemical parameters used to derive QSAR equation 25 for the inhibition of MMP-3 by thiazepine derivatives (**XXII**)

No.	X	Y	$\log 1/IC_{50}$ (Eq. 25)			σ^+
			Obsd.	Pred.	Δ	
1[a]	S	4-OCH_3	9.15	8.27	0.88	−0.78
2	SO_2	4-OCH_3	8.16	8.27	−0.11	−0.78
3[a]	S	4-Br	8.00	6.90	1.10	0.15
4	SO_2	4-Br	7.05	6.90	0.15	0.15
5	S	2-CH_3,4-Br	7.06	7.36	−0.30	−0.16
6	S	4-OC_4H_9	8.18	8.32	−0.14	−0.81
7	SO_2	4-OC_4H_9	8.57	8.32	0.25	−0.81
8	S	4-C_3H_7	7.34	7.55	−0.21	−0.29
9	S	4-C_5H_{11}	7.60	7.55	0.05	−0.29
10	S	4-$O(CH_2)_2OCH_3$	7.77	7.55	0.22	−0.29
11	S	4-OC_6H_5	7.96	7.86	0.10	−0.50

[a] Not included in the derivation of QSAR 25.

a hydrogen bond between Leu-164 and the sulfonamide oxygen may develop.

10.2.2.4. MMP-7 inhibitors. *Inhibition of MMP-7 by hydroxamate derivatives containing hydantoin moiety (**XXIII**)*. Data obtained from Natchus et al.[132] (Table 30).

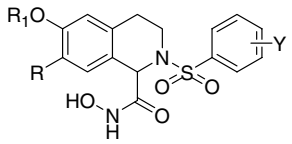


XXIII

$$\log 1/IC_{50} = 0.59(\pm 0.11)\mathrm{Clog}P - 1.94(\pm 0.56)\mathrm{MgVol} + 11.58(\pm 1.78), \quad (26)$$

$n = 13$, $r^2 = 0.937$, $s = 0.124$, $q^2 = 0.908$, $Q = 7.806$, $F = 74.365$.

*Inhibition of MMP-7 by tetrahydroisoquinoline-based sulfonamide hydroxamates (**XXIV**)*. Data obtained from Ma et al.[133] (Table 31).



XXIV

$$\log 1/IC_{50} = -0.58(\pm 0.26)\sigma_Y^+ + 5.03(\pm 0.14), \quad (27)$$

$n = 7$, $r^2 = 0.873$, $s = 0.145$, $q^2 = 0.758$, $Q = 6.441$, $F = 34.370$.

Negative coefficient of σ_Y^+ indicates that electron-releasing Y-group may enhance the inhibitory potency of the molecules.

Table 30. Biological and physicochemical parameters used to derive QSAR equation 26 for the inhibition of MMP-7 by hydroxamate derivatives containing hydantoin moiety (**XXIII**)

No.	X	Y	Z	$\log 1/IC_{50}$ (Eq. 26)			Clog P	MgVol
				Obsd.	Pred.	Δ		
1	H	CH_3	OCH_3	5.74	5.71	0.03	−0.92	2.75
2[a]	H	CH_3	OC_2H_5	5.12	5.74	−0.62	−0.39	2.89
3	H	CH_3	$O(CH_2)_2CH_3$	5.59	5.78	−0.19	0.14	3.03
4	H	CH_3	$O(CH_2)_3CH_3$	5.80	5.82	−0.02	0.67	3.18
5	H	CH_3	$OCH_2CH(CH)_2$	5.64	5.47	0.17	−0.43	3.02
6	H	CH_3	$O(CH_2)_2OCH_3$	5.04	4.98	0.06	−1.03	3.09
7[a]	H	CH_3	OC_6H_5	6.51	5.93	0.58	1.01	3.22
8	H	CH_3	O-4-Pyridyl	5.13	5.13	0.00	−0.48	3.18
9	SCH_3	H	$O(CH_2)_3CH_3$	6.07	6.05	0.02	1.61	3.34
10	$(CH_3)_2$	H	$O(CH_2)_3CH_3$	6.35	6.34	0.01	1.83	3.26
11	H	$CH_2CH{=}CH_2$	$O(CH_2)_2CH_3$	5.59	5.77	−0.18	0.92	3.27
12	H	$CH_2CH{=}CH_2$	$O(CH_2)_3CH_3$	6.00	5.81	0.19	1.44	3.41
13	H	$CH_2CH{=}CH_2$	$O(CH_2)_2OCH_3$	4.96	4.97	−0.01	−0.25	3.33
14	H	$CH_2CH_2CH_3$	$O(CH_2)_3CH_3$	5.92	5.89	0.03	1.73	3.46
15	H	$CH_2CH_2CH_3$	$O(CH_2)_2OCH_3$	4.96	5.06	−0.10	−0.03	3.38

[a] Not included in the derivation of QSAR 26.

Table 31. Biological and physicochemical parameters used to derive QSAR equation 27 for the inhibition of MMP-7 by tetrahydroisoquinoline-based sulfonamide hydroxamates (**XXIV**)

No.	R_1	R	Y	log 1/IC_{50} (Eq. 27)			σ_Y^+
				Obsd.	Pred.	Δ	
1	H	H	4-CH_3	4.98	5.21	−0.23	−0.31
2	H	H	4-NO_2	4.67	4.57	0.10	0.79
3	H	H	2-Cl, 5-Cl	4.67	4.75	−0.08	0.48
4	CH_2Ph	H	H	5.15	5.03	0.12	0.00
5[a]	CH_2Ph	H	4-CH_3	4.92	5.21	−0.29	−0.31
6	CH_2Ph	H	4-OCH_3	5.62	5.48	0.14	−0.78
7	H	OCH_3	H	4.97	5.03	−0.06	0.00
8	H	OCH_3	4-OCH_3	5.50	5.48	0.02	−0.78

[a] Not included in the derivation of QSAR 27.

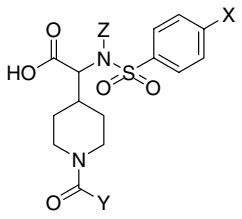
10.2.2.5. MMP-8 inhibitors. *Inhibition of MMP-8 by sulfonamide derivatives (**XIV**)*. Data obtained from Martin et al.[123] (Table 32).

$$\log 1/IC_{50} = 0.35(\pm 0.19)\mathrm{Clog}P - 1.18(\pm 0.47)I_{R2} + 7.29(\pm 0.51), \quad (28)$$

$n = 17$, $r^2 = 0.841$, $s = 0.377$, $q^2 = 0.739$, $Q = 2.432$, $F = 37.025$.

The indicator variable (I_{R2}) takes the value of 1 for the presence of CH_3 group and 0 for the others in R_2-position. The negative coefficient of I_{R2} indicates that CH_3 group may be avoided over the other substituents at R_2-position.

*Inhibition of MMP-8 by carboxylic acid derivatives (**XXV**)*. Data obtained from Pikul et al.[134] (Table 33).



XXV

Table 32. Biological, physicochemical, and structural parameters used to derive QSAR equations 28 and 39 for the inhibition of MMP-8 and MMP-13, respectively, by sulfonamide derivatives (**XIV**)

No.	R	X	R_1	R_2	log 1/IC_{50} (Eq. 28)			log 1/IC_{50} (Eq. 39)			Clog *P*	I_{R2}
					Obsd.	Pred.	Δ	Obsd.	Pred.	Δ		
1[a]	Isopropyl	Piperidinyl	Methyl	Methyl	7.00	6.16	0.84	—	—	—	0.13	1
2	Isopropyl	Piperidinyl	Methyl	Ethyl	7.00	7.52	−0.52	—	—	—	0.65	0
3	Isopropyl	Piperidinyl	Methyl	Ph(4-OMe)	7.70	8.00	−0.30	—	—	—	2.01	0
4	Isopropyl	Piperidinyl	Methyl	Dansyl	8.00	8.49	−0.49	—	—	—	3.41	0
5	Isopropyl	$N(Me)_2$	Methyl	Methyl	5.40	6.13	−0.73	5.70	5.97	−0.27	0.04	1
6	Cyclopentyl	Piperidinyl	Methyl	Methyl	6.70	6.38	0.32	6.40	6.18	0.22	0.76	1
7	Cyclopentyl	Piperidinyl	Methyl	Ethyl	8.00	7.75	0.25	7.40	7.35	0.05	1.29	0
8	Cyclopentyl	Piperidinyl	Methyl	Ph(4-OMe)	8.52	8.22	0.30	7.70	7.76	−0.06	2.64	0
9	Cyclopentyl	Piperidinyl	Methyl	Dansyl	8.70	8.72	−0.02	8.10	8.17	−0.07	4.04	0
10	Cyclopentyl	Piperidinyl	Methyl	Naphthalyl	8.40	8.58	−0.18	8.10	8.06	0.04	3.65	0
11	Cyclopentyl	Piperidinyl	*n*-Propyl	Methyl	7.05	6.75	0.30	6.70	6.50	0.20	1.82	1
12	Cyclopentyl	Piperidinyl	Cyclopentyl	Methyl	6.70	6.90	−0.20	6.70	6.62	0.08	2.23	1
13[a,b]	Cyclopentyl	Piperidinyl	Cyclopropyl	Methyl	7.40	6.51	0.89	7.00	6.29	0.71	1.11	1
14	Cyclopentyl	Piperidinyl	Isopropyl	Methyl	7.00	6.68	0.32	6.22	6.44	−0.22	1.60	1
15	Cyclopentyl	Piperidinyl	Methyl	Isopropyl	8.05	7.85	0.20	7.40	7.45	−0.05	1.60	0
16	Cyclopentyl	Piperidinyl	Methyl	Ph(4-Cl)	8.40	8.42	−0.02	8.00	7.92	0.08	3.18	0
17	Cyclopentyl	Piperidinyl	Methyl	$N(Me)_2$	8.00	7.55	0.45	7.40	7.19	0.21	0.74	0
18	Cyclopentyl	Piperidinyl	Methyl	CF_3	8.00	7.95	0.05	7.40	7.53	−0.13	1.87	0
19[a,b]	Cyclopentyl	Morpholinyl	Methyl	Methyl	7.70	6.39	1.31	7.10	6.19	0.91	0.77	1
20	Cyclopentyl	Morpholinyl	Methyl	Ph(4-OMe)	8.52	8.23	0.29	7.70	7.76	−0.06	2.65	0

[a] Not included in the derivation of QSAR 28.
[b] Not included in the derivation of QSAR 39.

Table 33. Biological and physicochemical parameters used to derive QSAR equations 29 and 43 for the inhibition of MMP-8 and MMP-13 by carboxylic acid derivatives (**XXV**)

No.	X	Y	Z	$\log 1/IC_{50}$ (Eq. 29)			$\log 1/IC_{50}$ (Eq. 43)			$C\pi_X$	CMR_X	CMR_Y
				Obsd.	Pred.	Δ	Obsd.	Pred.	Δ			
1	C_6H_4-4-OCH_3	OCH_3	H	8.17	8.55	−0.38	7.53	7.76	−0.23	1.88	3.13	0.62
2	C_6H_4-4-OCH_3	OCH_2CH_3	H	8.57	8.55	0.02	8.27	8.21	0.06	1.88	3.13	1.08
3	C_6H_4-4-OCH_3	$OCH(Me)_2$	H	8.82	8.55	0.27	9.00	8.67	0.33	1.88	3.13	1.54
4	C_6H_4-4-OCH_3	$OC(Me)_3$	H	8.92	8.55	0.37	9.15	8.97	0.18	1.88	3.13	1.86
5	C_6H_4-4-OCH_3	$OC(Me)_3$	H(R)	8.82	8.55	0.27	9.40	9.12	0.28	1.88	3.13	2.01
6[b]	C_6H_4-4-OCH_3	$OC(Me)_3$	H(S)	8.52	8.55	−0.03	8.16	9.12	−0.96	1.88	3.13	2.01
7[b]	C_6H_4-4-OCH_3	$CH_2CH(Me)_2$	H	8.28	8.55	−0.27	7.86	8.97	−1.11	1.88	3.13	1.86
8	C_6H_4-4-OCH_3	Morpholine	H	8.52	8.55	−0.03	8.74	9.31	−0.57	1.88	3.13	2.20
9	C_6H_4-4-OCH_3	$O(CH_2)_2OCH_3$	H	8.47	8.55	−0.08	8.46	8.82	−0.36	1.88	3.13	1.70
10[a]	C_6H_4-4-SCH_3	$O(CH_2)_2OCH_3$	H	8.74	9.76	−1.02	9.00	8.93	0.07	2.46	3.78	1.70
11	C_6H_5	$O(CH_2)_2OCH_3$	H	7.35	7.40	−0.05	7.26	7.22	0.04	1.89	2.51	1.70
12	OC_6H_5	$O(CH_2)_2OCH_3$	H	7.59	7.68	−0.09	6.85	7.05	−0.20	2.10	2.66	1.70
13	$O(CH_2)_3CH_3$	$O(CH_2)_2OCH_3$	H	6.53	6.46	0.07	6.10	6.00	0.10	1.86	2.01	1.70
14	C_6H_4-4-OCH_3	$O(CH_2)_2OCH_3$	CH_3	8.44	8.55	−0.11	8.62	8.82	−0.20	1.88	3.13	1.70
15	C_6H_4-4-OCH_3	$O(CH_2)_2OCH_3$	3-Picolyl	8.49	8.55	−0.06	8.52	8.82	−0.30	1.88	3.13	1.70
16	C_6H_4-4-OCH_3	$O(CH_2)_2OCH_3$	$(CH_2)_2OCH_3$	8.62	8.55	0.07	9.00	8.82	0.18	1.88	3.13	1.70
17[b]	C_6H_4-4-OCH_3	$O(CH_2)_2OCH_3$	H	9.30	8.55	0.75	9.40	8.82	0.58	1.88	3.13	1.70

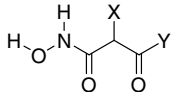
[a] Not included in the derivation of QSAR 29.
[b] Not included in the derivation of QSAR 43.

$$\log 1/IC_{50} = 1.86(\pm 0.36)CMR_X + 2.73(\pm 1.08), \quad (29)$$

$n = 15$, $r^2 = 0.906$, $s = 0.205$, $q^2 = 0.881$, $Q = 4.644$, $F = 125.298$. $C\pi_X$ versus CMR_X: $r = 0.229$.

$C\pi_X$ and CMR_X are the calculated hydrophobicity and the calculated molar refractivity of the X-substituents, respectively. Since CMR_X is a measure of the bulk of the X-substituents, the positive coefficient with this term indicates that molecules are occurring in polar space in the enzyme, not hydrophobic space. A positive coefficient might also suggest an interaction depending on the polarizability of the X-substituents. No term appears for Y- and Z-substituents.

*Inhibition of MMP-8 by nonpeptidic malonic acid hydroxamates (**XXVI**)*. Data obtained from von Roedern et al.[135] (Table 34).



XXVI

$$\log 1/K_i = 0.73(\pm 0.15)CMR_Y + 3.09(\pm 0.48), \quad (30)$$

$n = 12$, $r^2 = 0.923$, $s = 0.322$, $q^2 = 0.889$, $Q = 2.984$, $F = 119.870$.

A positive coefficient of CMR_Y (calculated molar refractivity of Y-substituents) might suggest an interaction depending on the polarizability of the Y-substituents.

10.2.2.6. MMP-9 inhibitors. *Inhibition of MMP-9 by 3-substituted anthranilate hydroxamic acids (**XXVII**)*. Data obtained from Levin et al.[136] (Table 35).

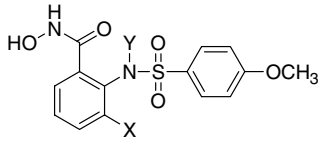
Table 34. Biological and physicochemical parameters used to derive QSAR equation 30 for the inhibition of MMP-8 by nonpeptidic malonic acid hydroxamates (**XXVI**)

No.	X	Y	$\log 1/K_i$ (Eq. 30)			CMR_Y
			Obsd.	Pred.	Δ	
1	Isobutyl	OCH_2CH_3	3.72	3.88	−0.16	1.08
2	C_6H_5	OCH_2CH_3	4.01	3.88	0.13	1.08
3	$CH_2C_6H_5$	OCH_2CH_3	4.28	3.88	0.40	1.08
4	$(CH_2)_2C_6H_5$	OCH_2CH_3	3.72	3.88	−0.16	1.08
5	$CH_2C_6H_5$	*N*-Morpholide	4.30	4.70	−0.40	2.20
6	$CH_2C_6H_5$	$NHCH_2C_6H_5$	5.51	5.54	−0.03	3.34
7	$(CH_2)_2C_6H_5$	$NHCH_2C_6H_5$	5.64	5.54	0.10	3.34
8	Isobutyl	$NH(CH_2)_3C_6H_5$	6.27	6.22	0.05	4.27
9	$CH_2C_6H_5$	$NH(CH_2)_3C_6H_5$	6.25	6.22	0.03	4.27
10	$(CH_2)_2C_6H_5$	$NH(CH_2)_3C_6H_5$	6.31	6.22	0.09	4.27
11	OH	$NH(CH_2)_3C_6H_5$	5.64	6.22	−0.58	4.27
12	Isobutyl	NH-*n*-octyl	6.62	6.08	0.54	4.08

Table 35. Biological and physicochemical parameters used to derive QSAR equations 31 and 41 for the inhibition of MMP-9 and MMP-13, respectively, by 3-substituted anthranilate hydroxamic acids (**XXVII**)

No.	X	Y	$\log 1/IC_{50}$ (Eq. 31)			$\log 1/IC_{50}$ (Eq. 41)			Clog *P*
			Obsd.	Pred.	Δ	Obsd.	Pred.	Δ	
1[a]	H	$CH_2C_6H_5$	6.19	7.56	−1.37	6.26	6.61	−0.35	1.68
2[b]	CH_3	$CH_2C_6H_5$	7.64	7.47	0.17	7.30	6.42	0.88	1.84
3	CH_3	CH_2-3-pyridyl	8.30	8.33	−0.03	8.10	8.27	−0.17	0.34
4	OCH_3	$CH_2C_6H_5$	7.64	7.54	0.10	6.86	6.58	0.28	1.71
5	Cl	$CH_2C_6H_5$	7.51	7.50	0.01	—	—	—	1.78
6	NO_2	$CH_2C_6H_5$	7.89	7.98	−0.09	7.38	7.53	−0.15	0.94
7	$N(CH_3)_2$	$CH_2C_6H_5$	7.19	7.43	−0.24	6.27	6.34	−0.07	1.90
8	CF_3	$CH_2C_6H_5$	7.57	7.56	0.01	6.87	6.63	0.24	1.67
9	$OCH_2CONHOH$	$CH_2C_6H_5$	8.70	8.59	0.11	9.00	8.85	0.15	−0.12
10	$OC(CH_3)_2CONHOH$	$CH_2C_6H_5$	8.40	8.24	0.16	8.22	8.08	0.14	0.50
11	$COOCH_3$	CH_2-3-pyridyl	8.22	8.42	−0.20	8.40	8.47	−0.07	0.19

[a] Not included in the derivation of QSAR 31.
[b] Not included in the derivation of QSAR 41.



XXVII

$$\log 1/IC_{50} = -0.58(\pm 0.15)\text{Clog}P + 8.53(\pm 0.19), \quad (31)$$

$n = 10$, $r^2 = 0.912$, $s = 0.150$, $q^2 = 0.856$, $Q = 6.367$, $F = 82.909$.

*Inhibition of MMP-9 by acyclic α-sulfonamide hydroxamates (**I**)*. Data obtained from Levin et al.[110] (Table 7).

$$\log 1/IC_{50} = 0.48(\pm 0.17)C\pi_X - 1.32(\pm 0.24)I_Y + 7.34(\pm 0.24), \quad (32)$$

$n = 14$, $r^2 = 0.951$, $s = 0.198$, $q^2 = 0.919$, $Q = 4.924$, $F = 106.745$.

The indicator variable (I_Y) applies to those compounds, which have Y = H. The negative coefficient of the indicator variable indicates that the presence of methyl or CH_2-3-pyridyl groups at Y-position will improve the activity.

*Inhibition of MMP-9 by sulfonylated amino acid hydroxamates (**VIII**)*. Data obtained from Scozzafava and Supuran[117] (Table 23).

$$\log 1/K_i = -0.37(\pm 0.15)\text{Clog}P + 0.58(\pm 0.10)\text{CMR} - 1.85(\pm 0.31)L_Y + 17.09(\pm 2.00), \quad (33)$$

$n = 36$, $r^2 = 0.902$, $s = 0.266$, $q^2 = 0.874$, $Q = 3.571$, $F = 98.177$. Clog *P* versus CMR: $r = 0.590$; Clog *P* versus L_Y: $r = 0.450$; CMR versus L_Y: $r = 0.205$.

CMR is the most important parameter, a measure of the bulk and the polarizability. A home-massage from the negative coefficient of Clog *P* is that the hydrophobicity is relatively unimportant and there is an interrelationship (Clog *P* versus CMR: $r = 0.590$). L_Y is the sterimol parameter for the length of Y-substituents. Its negative coefficient suggests that an increase in length of Y-substituents could be detrimental to the activity.

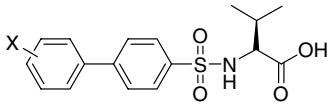
*Inhibition of MMP-9 by diketopiperazines (**IX**)*. Data obtained from Szardenings et al.[118] (Table 15).

$$\log 1/IC_{50} = -0.25(\pm 0.07)\text{CMR} + 9.31(\pm 0.93), \quad (34)$$

$n = 9$, $r^2 = 0.922$, $s = 0.089$, $q^2 = 0.877$, $Q = 10.787$, $F = 82.744$.

With respect to QSAR **34**, there is a significant correlation between Clog *P* and CMR ($r = 0.781$). But Clog *P* cannot replace CMR, because substituting Clog *P* for CMR in Eq. 35 gives a poor fit ($r^2 = 0.552$, $q^2 = 0.247$), which is not acceptable.

*Inhibition of MMP-9 by biphenylsulfonamide derivatives (**XXVIII**)*. Data obtained from O'Brien et al.[137] (Table 36).



XXVIII

$$\log 1/IC_{50} = 1.33(\pm 0.39)MR_{X\text{-}4} - 1.15(\pm 0.36)\sigma + 4.34(\pm 0.25), \quad (35)$$

$n = 12$, $r^2 = 0.916$, $s = 0.166$, $q^2 = 0.861$, $Q = 5.765$, $F = 49.071$. $\pi_{X\text{-}4}$ versus $MR_{X\text{-}4}$: $r = 0.182$; $\pi_{X\text{-}4}$ versus σ: $r = 0.265$; $MR_{X\text{-}4}$ versus σ: $r = 0.149$.

$MR_{X\text{-}4}$ is the molar refractivity of X-substituents at 4-position. Since MR is primarily a measure of the bulk of the substituent, the positive coefficient with this term indicates that molecules are contacting polar space in the enzyme, not hydrophobic space. It might also suggest an interaction depending on the polarizability of

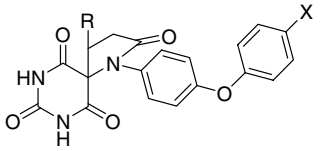
Table 36. Biological and physicochemical parameters used to derive QSAR equation 35 for the inhibition of MMP-9 by biphenylsulfonamide derivatives (**XXVIII**)

No.	X	$\log 1/IC_{50}$ (Eq. 35)			$MR_{X\text{-}4}$	σ
		Obsd.	Pred.	Δ		
1	H	4.59	4.47	0.12	0.10	0.00
2	4-F	4.19	4.39	−0.20	0.09	0.06
3	4-Br	5.10	5.25	−0.15	0.89	0.23
4	3-Br	4.00	4.02	−0.02	0.10	0.39
5	4-Cl	4.80	4.87	−0.07	0.60	0.23
6	2-F,4-Br	5.31	5.19	0.12	0.89	0.29
7	4-Me	5.41	5.29	0.12	0.56	−0.17
8	4-OMe	5.66	5.70	−0.04	0.79	−0.27
9[a]	4-NH_2	4.70	5.82	−1.12	0.54	−0.66
10	4-CF_3	4.70	4.38	0.32	0.50	0.54
11	4-CN	4.23	4.42	−0.19	0.63	0.66
12	4-CHO	4.77	4.77	0.00	0.69	0.42
13	4-NO_2	4.42	4.42	0.00	0.74	0.78

[a] Not included in the derivation of QSAR 35.

the substituents. Negative coefficient of σ indicates that electron-releasing X-group may enhance the inhibitory potency of the molecules.

*Inhibition of MMP-9 by spiro-barbiturates (**XXIX**).* Data obtained from Kim et al.[75] (Table 37).



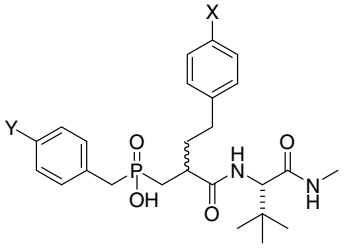
XXIX

$$\log 1/K_i = 1.19(\pm 0.46)B1_X + 7.07(\pm 0.66), \qquad (36)$$

$n = 6$, $r^2 = 0.928$, $s = 0.126$, $q^2 = 0.837$, $Q = 7.643$, $F = 51.556$. π_X versus $B1_X$: $r = 0.078$.

$B1_X$ is the sterimol parameter for X-substituents, which is the measure of minimum width suggesting a positive effect on the inhibition.

10.2.2.7. MMP-12 inhibitors. *Inhibition of MMP-12 by phosphinic acids (**XXX**).* Data obtained from Reiter et al.[138] (Table 38).



XXX

Table 37. Biological and physicochemical parameters used to derive QSAR equations 36 and 40 for the inhibition of MMP-9 and MMP-13, respectively, by spiro-barbiturates (**XXIX**)

No.	R	X	$\log 1/K_i$ (Eq. 36)			$\log 1/K_i$ (Eq. 40)			$B1_X$	π_X
			Obsd.	Pred.	Δ	Obsd.	Pred.	Δ		
1	H	H	8.33	8.26	0.07	8.33	8.49	−0.16	1.00	0.00
2	C_2H_5	H	8.14	8.26	−0.12	8.39	8.49	−0.10	1.00	0.00
3	H	Cl	9.14	9.21	−0.07	9.02	8.84	0.18	1.80	0.71
4	H	$COOCH_3$	8.92	9.02	−0.10	8.38	8.49	−0.11	1.64	−0.01
5	H	COOH	9.14	8.97	0.17	8.57	8.34	0.23	1.60	−0.32
6	H	OC_6H_5	8.72	8.68	0.04	9.48	9.51	−0.03	1.35	2.08

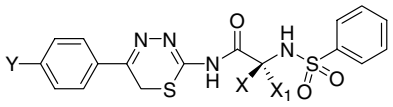
Table 38. Biological and physicochemical parameters used to derive QSAR equation 37 for the inhibition of MMP-12 by phosphinic acids (**XXX**)

No.	X	Y	$\log 1/IC_{50}$ (Eq. 37)			Clog P
			Obsd.	Pred.	Δ	
1	H	$CH_2C_6H_5$	8.09	8.21	−0.12	4.79
2	Cl	$CH_2C_6H_5$	8.77	8.60	0.17	5.50
3	H	$CH_2C_6H_4$-2-OCH_3	8.40	8.16	0.24	4.71
4	Cl	$CH_2C_6H_4$-2-OCH_3	8.30	8.56	−0.26	5.42
5	H	H	7.03	7.06	−0.03	2.72

$$\log 1/IC_{50} = 0.55(\pm 0.33)\text{Clog}P + 5.55(\pm 1.57), \quad (37)$$

$n = 5$, $r^2 = 0.904$, $s = 0.234$, $q^2 = 0.738$, $Q = 4.064$, $F = 28.250$.

*Inhibition of MMP-12 by 6H-1,3,4-thiadiazine derivatives (**XXXI**)*. Data obtained from Schröder et al.[139] (Table 39).



XXXI

$$\log 1/K_i = -0.39(\pm 0.14)L_Y - 0.23(\pm 0.12)I + 8.04(\pm 0.52), \quad (38)$$

$n = 13$, $r^2 = 0.844$, $s = 0.096$, $q^2 = 0.742$, $Q = 9.573$, $F = 27.051$.

L_Y is the sterimol parameter for the length of Y-substituents. The negative coefficient of L_Y suggests that an increase in the length of Y-substituents may be detrimental to the activity. The indicator variable (I) takes the value of 1 for the presence of Y = halogen and 0 for the others. The negative coefficient of I indicates that halogen group should be avoided at Y-position.

10.2.2.8. MMP-13 inhibitors. *Inhibition of MMP-13 by sulfonamide derivatives (**XIV**)*. Data obtained from Martin et al.[123] (Table 32).

$$\log 1/IC_{50} = 0.30(\pm 0.10)\text{Clog}P - 1.01(\pm 0.23)I_{R2} + 6.97(\pm 0.27), \quad (39)$$

$n = 14$, $r^2 = 0.959$, $s = 0.164$, $q^2 = 0.925$, $Q = 5.969$, $F = 128.646$.

The indicator variable (I_{R2}) takes the value of 1 for the presence of CH_3 group and 0 for the others in R_2 position.

*Inhibition of MMP-13 by spiro-barbiturates (**XXIX**)*. Data obtained from Kim et al.[75] (Table 37).

$$\log 1/K_i = 0.49(\pm 0.26)\pi_X + 8.49(\pm 0.24), \quad (40)$$

$n = 6$, $r^2 = 0.871$, $s = 0.186$, $q^2 = 0.728$, $Q = 5.016$, $F = 27.008$.

π_X is the hydrophobic parameter for X-substituents. The positive contribution of π_X suggests that higher hydrophobic X-substituents will increase the activity.

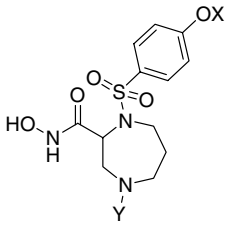
*Inhibition of MMP-13 by 3-substituted anthranilate hydroxamic acids (**XXVII**)*. Data obtained from Levin et al.[136] (Table 35).

$$\log 1/IC_{50} = -1.24(\pm 0.25)\text{Clog}P + 8.70(\pm 0.30) \quad (41)$$

$n = 9$, $r^2 = 0.952$, $s = 0.231$, $q^2 = 0.922$, $Q = 4.225$, $F = 138.834$.

Eq. 42 is very similar to 31. A negative coefficient with Clog$P$ suggests that less hydrophobic molecules will be more active.

*Inhibition of MMP-13 by diazepine-hydroxamates (**XXXII**)*. Data obtained from Levin et al.[140] (Table 40).



XXXII

Table 39. Biological, physicochemical, and structural parameters used to derive QSAR equation 38 for the inhibition of MMP-12 by 6*H*-1,3,4-thiadiazine derivatives (**XXXI**)

No.	X	X_1	Y	*R*/*S*	$\log 1/K_i$ (Eq. 38)			L_Y	*I*
					Obsd.	Pred.	*Δ*		
1[a]	H	CH_3	F	*S*	6.55	6.79	−0.24	2.65	1
2[a]	CH_3	H	F	*R*	6.46	6.79	−0.33	2.65	1
3	H	CH_3	Cl	*S*	6.28	6.45	−0.17	3.52	1
4	CH_3	H	Cl	*R*	6.49	6.45	0.04	3.52	1
5	H	CH_3	Br	*S*	6.36	6.33	0.03	3.82	1
6	CH_3	H	Br	*R*	6.47	6.33	0.14	3.82	1
7	H	CH_3	CN	*S*	6.43	6.41	0.02	4.23	0
8	CH_3	H	CN	*R*	6.44	6.41	0.03	4.23	0
9	H	CH_3	CH_3	*S*	6.96	6.93	0.03	2.87	0
10	CH_3	H	CH_3	*R*	7.05	6.93	0.12	2.87	0
11	H	$CH(Me)_2$	Cl	*S*	6.42	6.45	−0.03	3.52	1
12	$CH(Me)_2$	H	Cl	*R*	6.46	6.45	0.01	3.52	1
13	H	CH_3	NO_2	*S*	6.55	6.71	−0.16	3.44	0
14	H	CH_3	CF_3	*S*	6.52	6.54	−0.02	3.30	1
15	H	CH_3	OCH_3	*S*	6.47	6.50	−0.03	3.98	0

[a] Not included in the derivation of QSAR 38.

Table 40. Biological, physicochemical, and structural parameters used to derive QSAR equation 42 for the inhibition of MMP-13 by diazepine-hydroxamates (**XXXII**)

No.	X	Y	log 1/IC$_{50}$ (Eq. 42)			Cπ_Y	*I*
			Obsd.	Pred.	*Δ*		
1	CH_3	$CH_2C_6H_5$	7.19	7.35	−0.16	2.27	0
2	CH_3	COC_6H_5	8.66	8.80	−0.14	1.06	1
3	C_6H_5	COC_6H_5	8.89	8.80	0.09	1.06	1
4	CH_3	COC_6H_4-4-OCF_3	8.21	8.34	−0.13	2.39	1
5	CH_3	COC_6H_4-2-C_6H_5	8.34	8.15	0.19	2.95	1
6	CH_3	$COCH_2NHOCOC(CH_3)_3$	7.80	7.96	−0.16	0.52	0
7[a]	CH_3	$COCH_2NH_2 \cdot HCl$	7.34	8.43	−1.09	−0.85	0
8	CH_3	$COC(CH_3)_3$	7.96	7.92	0.04	0.63	0
9	CH_3	$COOC(CH_3)_3$	7.59	7.46	0.13	1.97	0
10	CH_3	$H \cdot HCl$	8.29	8.14	0.15	0.00	0
11	CH_3	$CONHC_6H_5$	7.77	7.76	0.01	1.11	0

[a] Not included in the derivation of QSAR 42.

$$\log 1/IC_{50} = -0.35(\pm 0.15)C\pi_Y + 1.03(\pm 0.27)I + 8.14(\pm 0.22), \quad (42)$$

$n = 10$, $r^2 = 0.925$, $s = 0.159$, $q^2 = 0.824$, $Q = 6.050$, $F = 43.167$.

Cπ_Y is the calculated hydrophobic parameter for Y-substituents. The indicator variable (*I*) takes the value of 1 for the presence of COPh or its derivatives and 0 for the others in Y-position. The positive coefficient of *I* indicates that the presence of COPh or its derivatives at Y-position will improve the activity as observed in Table 40.

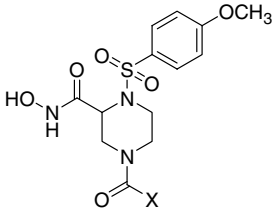
*Inhibition of MMP-13 by carboxylic acid derivatives (**XXV**)*. Data obtained from Pikul et al.[134] (Table 33).

$$\log 1/IC_{50} = -2.67(\pm 1.42)C\pi_X + 2.55(\pm 0.57)CMR_X + 0.98(\pm 0.55)CMR_Y + 4.21(\pm 2.65), \quad (43)$$

$n = 15$, $r^2 = 0.906$, $s = 0.341$, $q^2 = 0.799$, $Q = 2.792$, $F = 35.341$.

Cπ_X is the calculated hydrophobicity of the X-substituents, whereas CMR_X and CMR_Y are the molar refractivities of X- and Y-substituents, respectively. No term appears for Z-substituents.

*Inhibition of MMP-13 by amide-substituted piperazine derivatives (**XXXIII**)*. Data obtained from Cheng et al.[9] (Table 41).



XXXIII

$$\log 1/IC_{50} = 0.62(\pm 0.21)\text{Clog}P - 0.72(\pm 0.18)CMR + 15.30(\pm 1.73), \quad (44)$$

$n = 10$, $r^2 = 0.925$, $s = 0.157$, $q^2 = 0.842$, $Q = 6.127$, $F = 43.167$.

Table 41. Biological and physicochemical parameters used to derive QSAR equation 44 for the inhibition of MMP-13 by amide-substituted piperazine derivatives (**XXXIII**)

No.	X	log 1/IC$_{50}$ (Eq. 44)			Clog *P*	CMR
		Obsd.	Pred.	*Δ*		
1	CH_3	9.00	9.07	−0.07	−0.15	8.58
2	*n*-C_5H_{11}	8.77	9.04	−0.27	1.96	10.43
3	*c*-C_6H_{11}	8.82	8.78	0.04	1.88	10.72
4	$CH(OH)CH(Me)_2$	9.00	8.85	0.15	1.30	10.12
5	$CH_2OC_6H_5$	8.68	8.50	0.18	2.03	11.24
6	C_6H_5	8.52	8.56	−0.04	1.40	10.63
7	Thiophen-2-yl	8.72	8.56	0.16	1.18	10.43
8	Furan-2-yl	8.60	8.61	−0.01	0.58	9.84
9	5-CH_3-C_2N_2S-4-yl	7.68	7.71	−0.03	−0.15	10.48
10	3-C_6H_5-5-CH_3-Isoxazol-4-yl	7.57	7.67	−0.10	2.26	12.60
11[a]	C_6H_4-4-C_6H_5	9.05	7.92	1.13	3.29	13.14

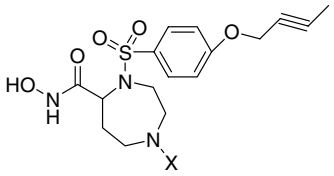
[a] Not included in the derivation of QSAR 44.

Table 42. Biological and physicochemical parameters used to derive QSAR equation 45 for the inhibition of MMP-13 by 1,4-diazepine-5-hydroxamic acids (**XXXIV**)

No.	X	$\log 1/IC_{50}$ (Eq. 45)			CMR
		Obsd.	Pred.	Δ	
1	COC_6H_5	8.40	8.31	0.09	12.35
2	$COCH_2CH_3$	7.70	7.88	−0.18	10.77
3	$COCH(CH_3)_2$	8.05	8.01	0.04	11.23
4[a]	$COCH_2OCH_3$	7.51	7.92	−0.41	10.92
5	$CH_2C_6H_5$	8.15	8.30	−0.15	12.32
6	$COOC(CH_3)_3$	8.30	8.17	0.13	11.85
7	H	7.49	7.50	−0.01	9.34
8	CH_3	7.68	7.62	0.06	9.81
9	CH_2CH_3	7.77	7.75	0.02	10.27

[a] Not included in the derivation of QSAR 45.

*Inhibition of MMP-13 by 1,4-diazepine-5-hydroxamic acids (**XXXIV**)*. Data obtained from Zask et al.[141] (Table 42).

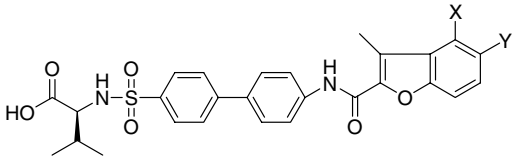


XXXIV

$$\log 1/IC_{50} = 0.27(\pm 0.10)CMR + 4.97(\pm 1.06), \quad (45)$$

$n = 8$, $r^2 = 0.889$, $s = 0.118$, $q^2 = 0.812$, $Q = 7.992$, $F = 48.054$. Clog P versus CMR: $r = 0.686$.

10.2.2.9. MMP-14 inhibitors. *Inhibition of MMP-14 by benzofuran derivatives (**XXXV**)*. Data obtained from Li et al.[77] (Table 43).



XXXV

$$\log 1/IC_{50} = -0.65(\pm 0.22)Clog P + 8.54(\pm 1.31), \quad (46)$$

$n = 7$, $r^2 = 0.920$, $s = 0.069$, $q^2 = 0.872$, $Q = 13.899$, $F = 57.500$.

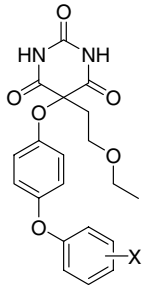
*Inhibition of MMP-14 by phosphinic pseudo-tripeptides (**XI**)*. Data obtained from Vassiliou et al.[121] (Table 17).

$$\log 1/K_i = 1.46(\pm 0.74)CMR - 12.68(\pm 9.85), \quad (47)$$

$n = 5$, $r^2 = 0.928$, $s = 0.224$, $q^2 = 0.873$, $Q = 4.304$, $F = 38.667$.

An interesting observation was made by the comparison of compounds **3**, **4**, and **5** illustrating the influence of a heteroatom in the γ position of the P1′ side chain. As compared to a carbon atom (compound **3**, Table 17), the presence of an oxygen in this position decreases the inhibitory potency (compound **4**, Table 17), while a sulfur significantly increases the potency of inhibition (compound **5**, Table 17).[121] This is also supported by our QSAR **47**, because the CMR of these three compounds is in the following order: compound **3** > compound **4** < compound **5** (Table 17).

*Inhibition of MMP-14 by pyrimidinetrione derivatives (**XXXVI**)*. Data obtained from Blagg et al.[142] (Table 44).



XXXVI

Table 43. Biological and physicochemical parameters used to derive QSAR equation 46 for the inhibition of MMP-14 by benzofuran derivatives (**XXXV**)

No.	X	Y	$\log 1/IC_{50}$ (Eq. 46)			Clog P
			Obsd.	Pred.	Δ	
1	OCH_3	Br	4.82	4.74	0.08	5.87
2	OCH_3	I	4.52	4.60	−0.08	6.08
3	OCH_3	Cl	4.91	4.84	0.07	5.72
4	OCH_3	CH_3	4.82	4.85	−0.03	5.69
5	OCH_3	C_2H_5	4.52	4.51	0.01	6.22
6	OH	C_2H_5	4.80	4.87	−0.07	5.67
7	$OCH(CH_3)_2$	Cl	4.30	4.29	0.01	6.56

Table 44. Biological, physicochemical, and structural parameters used to derive QSAR equation 48 for the inhibition of MMP-14 by pyrimidinetrione derivatives (**XXXVI**)

No.	X	$\log 1/IC_{50}$ (Eq. 48)			Clog *P*	$B1_X$	*I*
		Obsd.	Pred.	Δ			
1	4-F	7.64	8.21	−0.57	3.11	3.35	1
2	3-F	7.22	7.48	−0.26	3.11	3.35	0
3	2-F	7.80	7.38	0.42	2.91	3.35	0
4	4-Cl	7.74	7.45	0.29	3.68	3.80	1
5	3-Cl	6.92	6.72	0.20	3.68	3.80	0
6	2-Cl	6.29	6.60	−0.31	3.45	3.80	0
7	4-CH_3	7.64	7.27	0.37	3.47	3.52	0
8	3-CH_3	7.30	7.27	0.03	3.47	3.52	0
9	2-CH_3	7.15	7.27	−0.12	3.47	3.52	0
10	4-Br	7.72	7.18	0.54	3.83	3.95	1
11	4-CF_3	6.82	7.09	−0.27	3.85	3.99	1
12	4-$C(CH_3)_3$	5.17	5.41	−0.24	4.79	4.60	0
13	4-C_6H_5	7.44	7.52	−0.08	4.86	3.71	0
14[a]	4-OCH_3	6.66	7.37	−0.71	2.89	3.35	0
15	4-SO2CH_3	5.06	5.00	0.06	1.33	4.03	0
16	4-CN	6.70	6.54	0.16	2.40	3.60	0
17	4-$CONH_2$	6.21	6.31	−0.10	1.48	3.50	0
18	4-$CONHCH_3$	6.19	6.32	−0.13	1.69	3.54	0
19[a]	4-CON(CH3)$_2$	5.03	6.06	−1.03	1.43	3.60	0

[a] Not included in the derivation of QSAR 48.

$$\log 1/IC_{50} = 0.50(\pm 0.20)\mathrm{Clog}P - 2.33(\pm 0.61)B1_X + 0.73(\pm 0.42)I + 13.73(\pm 2.10), \quad (48)$$

$n = 17$, $r^2 = 0.877$, $s = 0.333$, $q^2 = 0.752$, $Q = 2.811$, $F = 30.897$. Clog *P* versus $B1_X$: $r = 0.384$.

$B1_X$ is the sterimol parameter for X-substituents, which is the measure of minimum width and suggests a negative effect on the inhibition. The indicator variable *I* takes the value of 1 for the presence of halogen at X-4. The positive coefficient of *I* indicates that the presence of halogen at X-4 position will improve the activity.

10.2.3. Validation of QSAR. The real utility of a QSAR model is in its ability to accurately predict the modeled property for new compounds. Thus, the validation of QSAR models is absolutely essential for its successful application and interpretation. A comparison of the statistics of QSAR (**1**)–(**48**) obtained from multi-regression analyses (MRA) has been shown in Table 45. All the QSARs are found to be statistically significant. The following approaches have been used for the validation of QSAR (**1**)–(**48**):

- *Fraction of the variance*. It is important to note that a QSAR model must have to explain a sufficiently high fraction of the variance for any data set. The fraction of the variance of an MRA model is expressed by r^2 (measure of the goodness of fit between model-predicted and experimental values). It is believed that the closer the value of r^2 to unity, the better the QSAR model. The values of r^2 for QSAR models (**1**)–(**48**) are found from 0.827 to 0.973 (Table 45). The high values of r^2 confirmed that the high fraction of the variance (82.7–97.3%) has been explained by these QSAR models. According to the literature, the predictive QSAR model must have $r^2 > 0.60$.[109,143]
- *Cross-validation test*. The cross-validated correlation coefficient (q^2) was obtained by using the leave-one-out procedure.[106] The values of q^2 for QSAR models (**1**)–(**48**) are 0.718–0.941 (Table 45). The high values of q^2 validate these QSAR models. In the literature, it must be greater than 0.50.[109,143]
- *Standard deviation (s)*. *s* is the standard deviation about the regression line. This is a measure of how well the function derived by the QSAR analysis predicts the observed biological activity. The smaller the value of *s* the better is the QSAR. The values of *s* for QSAR models (**1**)–(**48**) are 0.046–0.548 (Table 45).
- *Quality factor or quality ratio (Q)*. Chance correlation, due to the excessive number of parameter (which increases also the *r* and *s* values), is detected by the examination of *Q* value (quality factor or quality ratio).[107] The values of *Q* for QSAR models (**1**)–(**48**) are 1.690–21.435 (Table 45).
- *Fischer statistics (F)*. Fischer statistic (*F*) is a value derived from *F*-test indicating the probability of a true relationship, or the significance level of the MLR model. The *F*-value is the ratio between explained and unexplained variance for a given number of degree of freedom. The larger the *F*-value the greater the probability that the QSAR equation is significant. The *F*-values for the QSAR models (**1**)–(**48**) are 21.974–216.222 (Table 45).
- All the QSAR models also fulfill the thumb rule condition, that is (number of data points)/(number of descriptors) $\geqslant 4$.

10.2.4. Overview. An analysis of our QSAR results on the inhibition of various compound series against

Table 45. Summary of critical variables in new QSAR equations 1–48 on MMP inhibitors

QSAR No.	MMP type	Compounds	n	r^2	S	q^2	Q	F	Descriptor coefficients				Intercept
									Hydrophobic[a]	Steric	Electronic[b]	Others	
1	1	Acyclic α-sulfonamide hydroxamates (**I**)	13	0.849	0.369	0.727	2.499	28.113	0.94 Clog P	—	—	−1.01 I_Y	4.72
2	1	Compound (**II**)	11	0.827	0.117	0.731	7.769	43.023	0.22 Clog P	—	—	—	3.25
3	1	P1′ modified *t*-butyl glycines (**III**)	8	0.973	0.200	0.939	4.930	216.222	−0.47 Clog P	—	—	—	8.51
4	1	Phosphinic acid derivatives (**IV**)	8	0.848	0.351	0.747	2.624	33.474	−0.87 Clog P	—	—	—	10.15
5	1	Quinoline derivatives (**V**)	20	0.891	0.187	0.724	5.048	43.596	1.61 Clog P −0.32 Clog P^2 [Clog $P_{(o)}$ = 2.481]	—	—	0.95 I_Y	4.15
6	1	3-OH-3-methyl-pipecolic hydroxamates (**VI**)	16	0.846	0.226	0.761	4.071	21.974	0.88 Clog P	−1.35 CMR	—	0.82 I_X	19.05
7	1	Phosphinic acid derivatives (**VII**)	9	0.850	0.141	0.747	6.539	39.667	—	0.21 CMR_{X-4}	—	—	5.04
8	1	Sulfonylated amino acid hydroxamates (**VIII**)	31	0.884	0.177	0.838	5.311	49.534	—	0.42 CMR −0.17 $B5_X$ −1.05 L_Y −1.97 $B1_Y$	—	—	15.24
9	1	Diketopiperazines (**IX**)	8	0.973	0.046	0.941	21.435	216.222	—	−0.21 CMR	—	—	10.36
10	1	Macrocyclic hydroxamic acids (**X**).	8	0.912	0.390	0.857	2.449	62.182	—	−6.47 MgVol	—	—	34.22
11	2	Phosphinic pseudo-tripeptides (**XI**)	5	0.936	0.162	0.781	5.969	43.875	1.24 Clog P	—	—	—	5.04
12	2	6-Oxohexahydro-pyrimidines (**XII**)	6	0.865	0.186	0.790	5.000	25.630	0.58 Clog P	—	—	—	7.80
13	2	P1′ modified phenylalanine analogues (**XIII**)	16	0.919	0.471	0.869	2.036	73.747	0.35 Clog P	—	—	−3.63 I_Y	7.61
14	2	Sulfonamide derivatives (**XIV**)	20	0.893	0.270	0.821	3.500	44.511	0.43 Clog P	—	—	−0.43 I_R +1.09 I_{R1}	4.75
15	2	Succinyl hydroxamates and their carboxylic analogues (**XV**)	28	0.881	0.453	0.847	2.073	59.227	−0.54 Clog P	—	—	1.05 I_X −1.37 I_Y	9.69
16	2	Macrocyclic hydroxamic acids (**XVI**).	11	0.858	0.548	0.799	1.690	54.380	—	−1.13 CMR	—	—	24.94
17	2	Sulfonylated amino acid hydroxamates (**VIII**)	39	0.908	0.233	0.884	4.090	115.145	—	0.41 CMR −0.18 L_X −1.17 L_Y	—	—	13.51
18	3	P1′ hydroxamate derivatives (**XVII**)	11	0.904	0.245	0.848	3.882	84.750	0.58 Clog P	—	—	—	6.57
19	3	Hydroxamic acids having modifications of the aryl substituent (**XVIII**)	12	0.857	0.313	0.806	2.958	59.930	0.64 Clog P	—	—	—	4.64
20	3	Sulfonamide derivatives (**XIV**)	19	0.836	0.380	0.745	2.405	40.780	0.50 Clog P	—	—	1.27 I_{R1}	4.43
21	3	*N*-Carboxyalkyl dipeptides containing substituted P1′ homophenylalanines (**XIX**)	18	0.893	0.241	0.834	3.921	38.947	0.53 Clog P	−0.64 L_{X-3}	—	−1.17 I	7.13
22	3	Succinyl hydroxamic acids (**XX**)	15	0.906	0.296	0.842	3.216	35.340	30.54 $C\pi_X$ −3.09$C\pi_X^2$ −0.49 $C\pi_Y$ [$C\pi_{X(o)}$ = 4.936]	—	—	—	−65.94
23	3	Succinyl hydroxamates and their carboxylic analogues (**XV**)	25	0.895	0.366	0.860	2.585	93.762	−0.53 Clog P	—	—	1.52 I_X	8.22
24	3	Thiadiazole urea methylamides (**XXI**)	8	0.836	0.324	0.718	2.824	30.585	—	0.53 CMR	—	—	1.98
25	3	Thiazepine derivatives (**XXII**)	9	0.860	0.212	0.759	4.373	43.000	—	—	−1.48 σ^+	—	7.12

(*continued on next page*)

Table 45 (*continued*)

QSAR No.	MMP type	Compounds	n	r^2	S	q^2	Q	F	Descriptor coefficients				Intercept
									Hydrophobic[a]	Steric	Electronic[b]	Others	
26	7	Hydroxamate derivatives containing hydantoin moiety (**XXIII**)	13	0.937	0.124	0.908	7.806	74.365	0.59 Clog P	−1.94 MgVol	—	—	11.58
27	7	Tetrahydroisoquinoline-based sulfonamide hydroxamates (**XXIV**)	7	0.873	0.145	0.758	6.441	34.370	—	—	$-0.58\sigma_Y^+$	—	5.03
28	8	Sulfonamide derivatives (**XIV**)	17	0.841	0.377	0.739	2.432	37.025	0.35 Clog P	—	—	−1.18 I_{R2}	7.29
29	8	Carboxylic acid derivatives (**XXV**)	15	0.906	0.205	0.881	4.644	125.298	—	1.86 CMR_X	—	—	2.73
30	8	Nonpeptidic malonic acid hydroxamates (**XXVI**)	12	0.923	0.322	0.889	2.984	119.870	—	0.73 CMR_Y	—	—	3.09
31	9	3-substituted anthranilate hydroxamic acids (**XXVII**)	10	0.912	0.150	0.856	6.367	82.909	−0.58 Clog P	—	—	—	8.53
32	9	Acyclic α-sulfonamide hydroxamates (**I**)	14	0.951	0.198	0.919	4.924	106.745	0.48 $C\pi_X$	—	—	−1.32 I_Y	7.34
33	9	Sulfonylated amino acid hydroxamates (**VIII**)	36	0.902	0.266	0.874	3.571	98.177	−0.37 Clog P	0.58 CMR −1.85 L_Y	—	—	17.09
34	9	Diketopiperazines (**IX**)	9	0.922	0.089	0.877	10.787	82.744	—	−0.25 CMR	—	—	9.31
35	9	Biphenylsulfonamide derivatives (**XXVIII**)	12	0.916	0.166	0.861	5.765	49.071	—	1.33 $MR_{X\text{-}4}$	−1.15 σ	—	4.34
36	9	Spiro-barbiturates (**XXIX**)	6	0.928	0.126	0.837	7.643	51.556	—	1.19 $B1_X$	—	—	7.07
37	12	Phosphinic acids (**XXX**)	5	0.904	0.234	0.738	4.064	28.250	0.55 Clog P	—	—	—	5.55
38	12	6*H*-1,3,4-Thiadiazine derivatives (**XXXI**)	13	0.844	0.096	0.742	9.573	27.051	—	−0.39 L_Y	—	−0.23 I	8.04
39	13	Sulfonamide derivatives (**XIV**)	14	0.959	0.164	0.925	5.969	128.646	0.30 Clog P	—	—	−1.01 I_{R2}	6.97
40	13	Spiro-barbiturates (**XXIX**)	6	0.871	0.186	0.728	5.016	27.008	0.49 π_X	—	—	—	8.49
41	13	3-Substituted anthranilate hydroxamic acids (**XXVII**)	9	0.952	0.231	0.922	4.225	138.834	−1.24 Clog P	—	—	—	8.70
42	13	Diazepine-hydroxamates (**XXXII**)	10	0.925	0.159	0.824	6.050	43.167	−0.35 $C\pi_Y$	—	—	1.03 I	8.14
43	13	Carboxylic acid derivatives (**XXV**)	15	0.906	0.341	0.799	2.792	35.341	−2.67 $C\pi_X$	2.55 CMR_X 0.98 CMR_Y	—	—	4.21
44	13	Amide-substituted piperazine derivatives (**XXXIII**)	10	0.925	0.157	0.842	6.127	43.167	0.62 Clog P	−0.72 CMR	—	—	15.30
45	13	1,4-Diazepine-5-hydroxamic acids (**XXXIV**)	8	0.889	0.118	0.812	7.992	48.054	—	0.27 CMR	—	—	4.97
46	14	Benzofuran derivatives (**XXXV**)	7	0.920	0.069	0.872	13.899	57.500	−0.65 Clog P	—	—	—	8.54
47	14	Phosphinic pseudo-tripeptides (**XI**)	5	0.928	0.224	0.873	4.304	38.667	—	1.46 CMR	—	—	−12.68
48	14	Pyrimidinetrione derivatives (**XXXVI**)	17	0.877	0.333	0.752	2.811	30.897	0.50 Clog P	−2.33 $B1_X$	—	0.73 I	13.73

[a] Clog $P_{(o)}$ = optimum value of Clog P; $C\pi_{X(o)}$ = optimum value of $C\pi_X$.
[b] $\sigma^+_{(o)}$ = optimum value of σ^+.

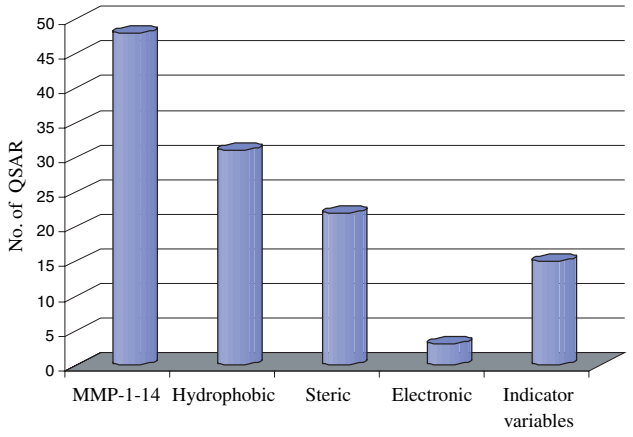


Figure 16. Contribution of different descriptors in the derivation of QSARs (**1**–**48**) for MMP-1–14.

MMP-1, -2, -3, -7, -8, -9, -12, -13, and -14 reveals a number of interesting points. The most important of these is hydrophobicity, which is one of the most important determinants of activity. Out of 48 QSAR, 31 contain a correlation between activity and hydrophobicity. A positive linear correlation is found in 19 equations (Eqs. 1, 2, 6, 11–14, 18–21, 26, 28, 32, 37, 39, 40, 44, and 48). The coefficient with the hydrophobic parameter varies considerably, from a low value of 0.22 (Eq. 2) to the high value of 1.24 (Eq. 11). These data suggest that activity might be improved by increasing compound hydrophobicity. A negative linear correlation is found in 11 equations (Eqs. 3, 4, 15, 22, 23, 31, 33, 41–43, and 46), and the coefficient ranges from −0.35 (Eq. 42) to −2.67 (Eq. 43). Less hydrophobic congeners in these compound families might display enhanced activity. Parabolic correlation with hydrophobicity is found in two equations (Eqs. 5 and 22). This may be an encouraging example, where the optimal hydrophobicity is well defined that is $\log P_{(o)} = 2.481$ and $\pi_{(o)} = 4.936$. We believe that this may be the predictive models to narrow the synthetic challenges in order to yield very specific MMP-1 and MMP-3 inhibitors. The second important parameter is molar refractivity, which is present in 16 QSAR.

Other parameters, sterimol, molar volume, and electronic also appear in several QSARs. In some cases, these parameters correlate all of the observed variation in activity, but they do not seem to play as important a role as hydrophobicity and molar refractivity for the data sets that we have examined. The contribution of different descriptors in the derivation of QSARs (**1**–**48**) has been shown in Figure 16.

11. MMP inhibitors in clinical trials

A number of MMP inhibitors are in various stages of clinical development especially for the treatment of cancer and arthritis, and listed in Table 46.

12. Conclusion

Matrix metalloproteinases are considered as promising targets for the treatment of cancer due to their strong involvement in malignant pathologies. Clinical/preclinical studies on MMP inhibition in tumor models brought positive results raising the idea that the development of strategies to inhibit MMPs may be proved to be a powerful tool to fight against cancer. Despite the known 3D structure of several catalytic domains of MMPs, the development of highly specific synthetic active-site-directed inhibitors of MMPs, which will enable one to differentiate the different members of this protease family, remains a strong challenge. Structural information as provided by X-ray structure can be used to improve the selectivity of inhibitors toward a particular MMP by optimizing the fit and the interactions of the potential inhibitor with the target MMP. However, the presence of an inherent flexibility in the MMP active-site limits dramatically the accurate modeling of MMP–inhibitor complexes. Thus, the development of specific MMPIs will need to combine the theoretical and experimental approaches to depict in each MMP the specific structural and dynamic features that can be exploited to obtain the desired selectivity. The application of the QSAR paradigm may be useful in elucidating the mechanisms of chemical–biological interaction for this enzyme. Our QSAR results show that hydrophobicity and molar refractivity are the two most important determinants of the activity. Combinatorial chemistry can be utilized to find whether the cooperative effects in inhibitor binding be exploited to identify selective inhibitors. For instance, it would be interesting to know how the P1, P2′, and P3′ preferences of different MMPs evolve when the size of the side chain in the P1′ position is systematically increased.

The advanced strategies' development for MMP inhibition will also be required to use the new tools introduced for assessing the efficiency of the different compounds in modulating MMP production or activity in cancer patients. Imaging techniques that allow in vivo analysis of MMP inhibition may be considered to be the fundamental tools for monitoring the effectiveness of drugs that are designed to target MMPs in cancer patients.[146] The identification of surrogate markers for MMP activity is also important.[147] The use of NMR analysis of MMPI complexes in solution is also important to characterize the motion existing both in the level of inhibitor and protein in the complex. The NMR study demonstrated the occurrence of two conformations of the complex in solution (MMP-1 in interaction with an inhibitor bearing a long side chain in the P1′ position), involving both slow and fast exchange between these distinct conformations.[148] The author speculates that motions in this complex through favorable entropic contributions compensate for the poor fit of the long side chain in the P1′ position in the S1′ pocket of MMP-1 and the resulting energetic cost of opening this pocket.

The importance of nutraceuticals in cancer prevention and treatment remains largely under-exploited, despite increasing evidence that these molecules have both

Table 46. MMP inhibitors in clinical trials

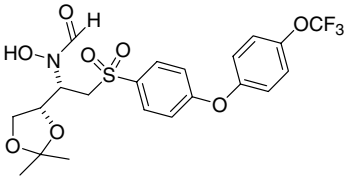
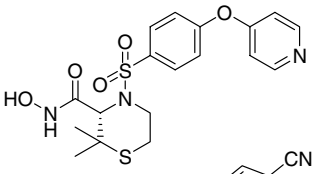
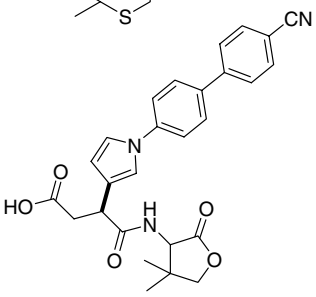
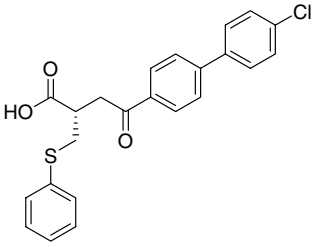
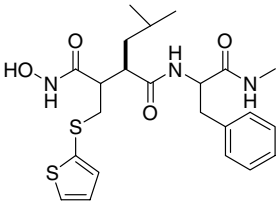
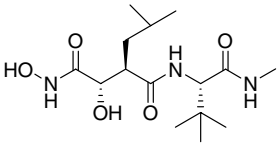
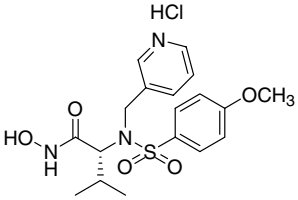
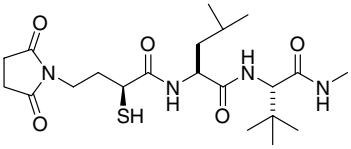
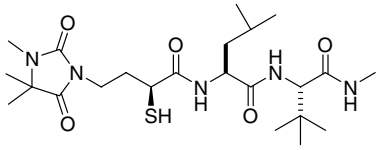
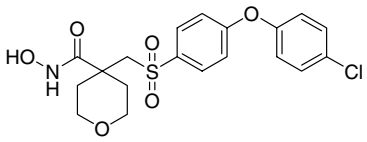
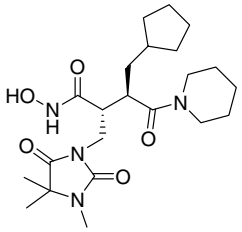
No.	MMP inhibitors	Structure	Company name	Comments	Status	Reference
1	ABT-518		Abbott	Cancer	Phase I	144
2	AG-3340 (Prinomastat)		Agouron	Cancer Macular degeneration	Phase III Phase II	7,15 7
3	AG-3433		Agouron	Cancer	Phase I	15
4	BAY 12-9566		Bayer	Cancer Arthritis	Phase III Phase II (withdrawn)	7,15 15
5	BB-94 (Batimastst)		British Biotech	Cancer	Phase II	15
6	BB-2516 (Marimastat)		British Biotech	Cancer	Phase III	7,15
7	BB-3644	Not Released	British Biotech	Cancer	Phase I	7
8	CGS-27023A		Novartis	Arthritis Cancer	Phase I Phase I	7 7
9	D-1927		Chiroscience	Cancer Inflammation	Preclinical Phase II	7 15

Table 46 (*continued*)

No.	MMP inhibitors	Structure	Company name	Comments	Status	Reference
10	D-2163 (BMS-275291)		Chiroscience	Cancer	Phase III	145
11	Metastat	Not Released	CollaGenex	Cancer	Preclinical	7
12	RS-130,830		Roche Bioscience	Arthritis	Phase II	15
13	RO 32-3555		Roche	Arthritis	Phase III (withdrawn)	15

chemo-preventive and chemo-therapeutic ability. The mechanisms of inhibition of MMPs by bio-drugs may be of significant importance to understanding the mechanism by which nutraceuticals elicit their anti-tumoral and anti-metastatic effects.

References and notes

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Rajeshwar P. Verma was born in 1966 in Barh (India). He received his M.Sc. (1988) and Ph.D. (1992) degrees in chemistry from Magadh University, Bodh-Gaya. He spent a year at the same university as a postdoctoral fellow with Professor K. S. Sinha. He joined Roorkee University (now IIT Roorkee) as a research associate and worked with Professor S.M. Sondhi (1993–1997). He also worked as a Lecturer of Chemistry at Gurukula Kangri University, Hardwar (1994–1995). He won a Research Associateship Award in December 1994 from the Council of Scientific and Industrial Research, New Delhi (India). In 1997, he moved to Pomona College to join the renowned QSAR research group of Professor Corwin Hansch and Cynthia Selassie, working as a postdoctoral research associate. Dr. Verma's research interests include the following: isolation, characterization, and synthesis of natural products derived from medicinal plants; chemistry of isothiocyanates; synthesis of biologically important heterocycles and phenolic compounds; quantitative structure–activity relationships (QSAR) and computer-assisted drug design.

Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in organic chemistry from New York University in 1944. After working with the Du Pont Co., first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich, Switzerland, with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. He is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.