An Updated Patent Therapeutic Agents Targeting MMPs

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Abstract: The traditional consensus that matrix metalloproteinases (MMPs) has correlation with various pathological and physiological processes led to the exploitation of a vast number of natural or synthetic broad-spectrum MMP inhibitors (MMPIs) for the prophylaxis or treatment of various MMP-related disorders, such as autoimmune, inflammatory, cardiovascular, neurodegenerative, respiratory diseases, and malignant cancer as well. Yet the unsatisfactory preclinical and/or clinical results motivated further investigation of the physiological roles of certain MMP subtypes. Despite the intricate and complicated MMP functions in normal physiology and disease pathology, the effort of designing specific inhibitors that can selectively target certain MMP family members for individualized therapy is ongoing and remains an arduous task. Success will rely on continued insight into the biological roles of these multifaced proteases. In our previous effort, we summarized various MMPIs that have entered preclinical or clinical trials as well as the patents in regard to MMPIs (Recent Pat Anticancer Drug Discov. 2010; 5(2): 109-41). In our on-going review, to illustrate the major challenges in MMP validation as druggable targets, we highlighted the physiological and pathological roles of representative MMPs, with an emphasis on description of the newly emerging MMPI-based patents, in particular, the inhibitors containing sulfonamide or sulfone motif. By analyzing the structural characteristics and selectivity profiles of these supplementary inhibitors, we hereby described their pharmaceutical application, and also expanded the strategies for potent MMPI design.

Keywords: Drug design, matrix metalloproteinases (MMPs), MMPI, patent, specific, selectivity.

INTRODUCTION

The matrix metalloproteinases (MMPs), also called matrixins, are a group of genetically distinct but structurally related calcium-dependent zinc-containing endopeptidases that are involved in the degradation and repair of major macromolecular components of extracellular matrix (ECM), connective tissue and cell surface-bound molecules [1]. They are naturally occurring proteolytic enzymes found in most mammals that are secreted especially by mesenchymal cells, macrophages and polymorphonuclear leukocytes [2]. A large set of experimental data indicated that MMPs play essential roles in the processes of tissue remodeling and repair, morphogenesis, angiogenesis, embryonic development, apoptosis, ovulation, neural development, wound healing, chemotherapy-induced alimentary tract (AT) mucositis, cell adhesion and proliferation as well [3-5]. Moreover, these enzymes have frequently been detected in human tumor specimens and their production and/or misregulation has been associated with the tumor aggressiveness and poor prognosis [6, 7].

Under normal physiological conditions, the expression and activity of these enzymes are very low and strictly controlled by endogenous specific tissue inhibitors of metalloproteinases (TIMPs). Generally, there are a total of four TIMPs (TIMP-1, -2, -3, and -4) and these four protein inhibitors are able to control the proteolytic activity of all MMPs and mediate the stability of cells. However, in the presence of specific stimuli exemplified by cytokines and growth factor, the functions of MMP will be abnormally promoted in pathology, destroying the balances in the expression of MMPs and TIMPs. That is, over-expression or high activation of MMPs has been causally linked with the pathological destruction of connective tissue and the ensuing pathological disorders characterized by the breakdown of ECM components or connective tissues [1]. These diseases include cancer, osteoarthritis (OA), rheumatoid arthritis (RA), angiogenesis, chronic periodontitis, pulmonary emphysema, skin ulceration, atherosclerosis, gingivitis, central nervous system disease, type I diabetes, myocarditis and dilated cardiomyopathy, coronary artery disease, multiple sclerosis (MS), congestive heart failure, cardiovascular disease and so on [8-13]. On the basis of their primary roles in various oncologic events, the MMPs have been a highly active set of targets for the design of therapeutic agents to intervene the MMP-related pathological states, such as carcinogenesis and arthritis [14].

STRUCTURAL CHARACTERISTICS AND CLASSIFICATION OF MMPS

The MMP gene family consists of at least 26 structurally related members which can be broadly classified into five subfamilies based on the variation in their primary structure and function, substrate specificity, as well as their cellular sources: collagenase group (MMP-1, -8, -13, -18), gelatinase group (MMP-2, -9), stromelysin group (MMP-3, -10, -11),

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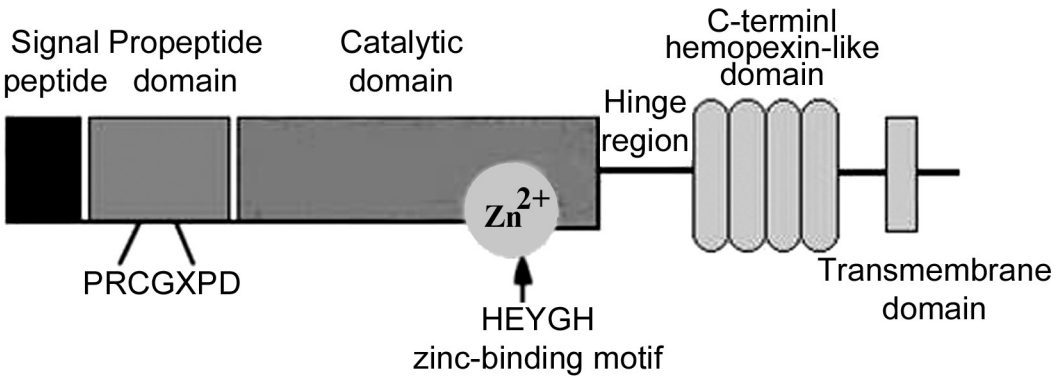


Fig. (1). Basic Structural Domain of MMPs.

membrane type (MT)-MMP group (MMP-14, -15, -16, -17), and a non-classified group (MMP-7, -12) [15].

The general structure of the MMPs consists of an archetypal secretory signal peptide, a prodomain that allows them to remain latent in extracellular area until they are activated via proteolytic cleavage, a catalytic domain with a highly conserved zinc-binding motif that is responsible for enzyme activity and, in the majority of cases, a hinge region, a C-terminal hemopexin-like domain, with the exception of MMP-7, -23, -26, that is linked to the catalytic domain by a hinge region and involved in substrate specificity as well as the transmembrane domain (see Fig. (**1**)). Among these domains, the hemopexin-homology domain is considered to promote interactions with substrate and thereby contribute to substrate specificity. In addition, the gelatinases (MMP-2 & -9) constitute a distinct subgroup of the MMPs family owing to the incorporation of three repeats of the fibronectin-like type II (FN2) motif inserting into the catalytic domain [16].

There are total six membrane-type MMPs (MT-MMPs) localized at the cell surface through a C-terminal transmembrane domain (MT1-, MT2-, MT3-, and MT5-MMP) and two glycosylphosphatidylinositol anchors (MT4- and MT6-MMP). The MT-MMPs and three secreted MMPs (MMP-11, -21, -28) also contain a furin-like enzyme recognition sequence not found in other family members. Furthermore, there are two unusual transmembrane MMPs (MMP-23A & -23B) that are anchored through the N-terminal segment and show identical amino acid sequence, despite being encoded by two distinct human genes [15].

PHYSIOLOGICAL OR PATHOLOGICAL ROLES OF REPRESENTATIVE MMPS

As illustrated, MMPs are originally defined by their ability to degrade the components of ECM, while ECM degradation is frequently associated with a poor prognosis in various pathologies. Additionally, it has established that specific MMP enzymes are associated with certain diseases, with no apparent effect on others. In this regard, inhibition of the over-regulation of specific MMPs may be of benefit to achieve positive intervention for the treatment of pathologic conditions. However, it should be emphasized that not all MMPs contribute to tumor progression. Certain member of MMPs, such as novel emerging non-matrix degrading functions of MMPs, might has not much bearing on tumorigenic effects [17], while others could act as a beneficial and/or protective role in some cancers, making them anti-targets for cancer therapy [18]. These pleiotropic functions might, to a great extent, account for the failure of most MMPIs in clinical trials. To achieve a comprehensive understanding of the causal relationship between MMPs and various pathological conditions, it is necessary to elucidate the physiological and pathophysiological roles of some identified members of MMP family.

MMP-13 (Collagenase-3)

Among MMP subtypes, MMP-13, almost expressed in cartilage and bone tissue, is considered as a cofactor relating to bone-absorption or cartilage, such as rheumatoid arthritis, osteoarthritis characterized by the degeneration of joint cartilage and adjacent bone that can cause pain and stiffness. This is because MMP-13 localizes in joints together with aggrecanase which proteolyses aggrecan which is a main component of articular cartilage, and that shows potent proteolytic activity against collagen II which is another main component of cartilage [19]. Considering MMP-13 shows a potent collagen degradation activity in contrast to other collagenases, it is thereby expected that inhibitor of MMP-13 might be useful as a prophylactic or therapeutic treating agent in the bone and joint diseases [20, 21]. Evidences also indicate that up-regulation of MMP-13 at the tumor-bone (TB) interface is important in tumor-induced osteolysis, suggesting that MMP-13 is also a potential therapeutic target for breast cancer bone metastasis [22]. In addition, by using western blot, immunohistochemical staining as well as *in situ* hybridization assays, Hernandez *et al.* [23] validated the presence of MMP-13 in progressive periodontal disease, with observable differences between periodontitis and healthy subjects, suggesting that MMP-13 inhibitors might be useful in the therapy of periodontal disease. More recently, studies from Meierjohann *et al.* show for the first time that knockdown of MMP-13 strongly enhanced pigmentation of melanocytes by using sh- and siRNA techniques, thereby inhibition MMP-13 can result in strong growth inhibition of melanocytes [24].

MMP-12 (Macrophage Elastase)

MMP-12 (human macrophage elastase, HME), like many other MMPs, is able to digest many macromolecules of the ECM (e.g. gelatin, fibronectin, laminin and especially elastin). Accumulated studies have revealed that MMP-12 could be related to tissue remodeling and degradation in some inflammatory processes and is involved in a number of

physiological or pathological situations, such as conversion of plasminogen into angiostatin, allergic airway inflammation, vascular remodeling or alteration, chronic obstructive pulmonary disease (COPD), emphysema, rheumatoid arthritis, as well as atherosclerosis [25-27]. For instance, studies from Hautamaki *et al*. demonstrated the absence of development of emphysema in MMP-12-deficient mice, which have been exposed for a long time to cigarette smoke, suggesting a predominant role of this enzyme in the occurrence and development of emphysema [28]. While investigation on disclosing macrophage involvement in rheumatoid arthritis revealed that elevated MMP-12 expression levels were observed in synovial tissues and fluids from patients with rheumatoid arthritis relative to those with osteoarthritis [29]. Another study by using DNA microarray technology also suggested that MMP-12 expression significantly correlated with local recurrence and metastatic disease in non-small cell lung cancer (NSCLC) patients. Therefore, it might serve as a prognostic indicator for early tumor relapse [30].

MMP-12, in particular, has been demonstrated to play a significant role in airway inflammation and remodeling. Recent studies have shown by immunohistochemistry that bronchoalveolar lavage (BAL) cells and bronchial lung biopsies from patients with moderate to severe COPD had greater MMP-12 expression than controls [31]. Similarly, other studies have demonstrated that there is increased MMP-12 expression and enzyme activity in induced sputum from patients with mild-moderate COPD compared to non-smokers, former smokers, or current smokers [32]. Based on this knowledge, MMP-12 can be considered as a valuable therapeutic target for exploring selective inhibitors that are useful for preventing and treating chronic respiratory pathologies, tumor metastasis, or other inflammatory diseases.

Gelatinases (MMP-2 & -9)

Among the MMPs, the gelatinase subgroup (MMP-2 & -9) constitute a distinct and unique subgroup because they are the only ones which contain FN2 domains inserted into their catalytic domains. The FN2 domains endow MMP-2 & -9 with specific degrading abilities on various constituents of the ECM, such as type IV collagen, which is the major component of vascular membranes, type V collagen, all types of denatured collagens (gelatins), and elastin, facilitating tumor intervention (e.g. invasion, metastasis and angiogenesis) [33]. Accordingly, many researchers focused on designing specific MMPIs with enhanced gelatinase selectivity through interacting with both the active sites as well as exosites like the collagen-binding FN2 domains of the enzyme [34, 35].

The gelatinase is also proved to play important roles in cardiovascular disorders including ischaemia/reperfusion injury, inflammatory heart disease, septic shock and pre-eclampsia. In addition, gelatinase appears to exert significant influence on propagating the brain tissue damage that occurs following an ischemic or hemorrhagic insult, thereby playing a crucial role in many diseases such as inflammation, as well as neurodegenerative and neurovascular diseases, most notably in stroke [36].

Now, a growing interest is focusing on the expression of gelatinases with cancer invasiveness, especially the growth and metastatic spread of tumors. Indeed, the metastatic spread of cancer via proteolytic degradation of host biomatrix poses one of the great challenges for the cancer therapy. An abundance of evidence indicates the involvement of MMPs in general, and gelatinases in particular, in local tumor growth, invasion, and metastatic spread of cancer to disseminated sites. Accordingly, gelatinase inhibition has been suggested as a promising non-cytotoxic therapeutic strategy for angiogenesis and/or tumor metastasis. For instance, elevated levels of gelatinases are correlated with human glioblastoma progression and the malignant degree, compared with low-grade brain tumors [37]. Study from Liu *et al.* demonstrated that osteopontin (OPN) knockdown could downregulate expression of MMP-2 and MMP-9, resulting in inhibition the malignant physiological behaviors of prostate cancer PC-3 cell. And else, IκB kinase-2 (IKK-2) may play a crucial role in OPN-induced MMP-2 and MMP-9 expressions via nuclear factor κB (NF-κB)-mediated signaling pathways [38]. Moreover, recent evidence suggests that gelatinases are involved in plaque rupture associated with atherosclerosis [39]. Furthermore, evidence suggests that direct or indirect effects of gelatinases on ion channels in the endothelium and vascular smooth muscle, and on other mechanisms of vascular relaxation/contraction [40].

Gelatinase A (MMP-2), which is localized in both tumor and vasculature cells, in particular, is intimately associated with tumor progression, at both the mRNA and protein level [41-43]. Besides, given MMP-2 is sensitive to oxidative stress, and has a proapoptotic role in the loss of retinal capillary cells in diabetes, and the activation of MMP-2 is under the control of superoxide, implying a possible use of MMP-2-targeted therapy to inhibit the development of diabetic retinopathy or cardiac diseases [44, 45]. And else, evidence revealed that MMP-2 is associated with the physiological process of myelination in the peripheral nervous system (PNS). Consequently, endogenous or exogenous modulation of MMP-2 activity may be a relevant target to enhance regeneration in demyelinating diseases of the PNS [46]. Additionally, to determine the potential involvement of certain MMPs and a membrane-type MMP in retinal pericyte death, investigation from Yang *et al.* demonstrated that increased MMP-2 activity compromises retinal pericyte survival possibly through MMP-2 action on ECM proteins and/or direct association of MMP-2 with integrins, which promotes apoptosis/anoikis by loss of cell contact with an appropriate ECM [47].

Compared to the well-defined MMP-2, MMP-9 (gelatinase B), which is secreted in the body in a latent form and involved in the cleavage of all types of denatured collagens and of native basement membrane proteins [48], seems to have more complicated functions. On one hand, high expression levels of MMP-9 are proved to have highly correlation with certain metastatic cancer since it requires proteolytic degradation of ECM components in basement membrane and stroma tissues, such as prostate cancer [49], nasopharyngeal carcinoma (NPC) [50], breast cancer [51], rectal carcinoma [52], NSCLC [53] and so on. In addition, MMP-9 has been shown to play an important role in key physiological and pathological brain processes such as cerebral ischemia, human stroke, as well as NMDA receptor (NMDAR)-dependent synaptic plasticity and memory [54, 55]. This is because up-regulation of MMP-9 increases the permeability

of the blood brain barrier (BBB), facilitates the infiltration of leukocytes into the central nervous system, and causes myelin sheath degradation and neuronal damage. Moreover, upon activation MMP-9 acts on many inflammatory substrates, and thus is suspected of contributing to the progression of cardiovascular disease, rheumatoid arthritis, and the subjects of this review, COPD and MS [56].

On the other hand, however, MMP-9 itself might be an anticancer enzyme at later stages of the carcinogenesis under certain circumstances. This is based on the fact that MMP-9 knockdown mouse model of multistage tumorigenesis demonstrated decreased carcinogenesis, whereas tumor formed in MMP-9-deficient mice were more aggressive [57]. One genetic data indicates that concomitant ablation of MMP-9 and the serine protease plasmin can result in lethal inflammatory mass lesions in the mouse colon model [58]. Evidence also suggests MMP-9 might function as a tumor suppressor in the process of colon cancer (CAC) [59]. These observations lead to the reconsideration of MMP-9 as a druggable target and, deeper understanding of MMP-9 is therefore remarkably warranted.

MMP-1

Among MMP subtypes, MMP-1 (human fibroblast collagenase) is the most ubiquitously expressed of all the interstitial collagenase and has a prominent role in initial cleavage of the ECM. An extensive body of evidence indicates that overexpression or high active of MMP-1 is usually associated with cancer, rheumatoid arthritis, pulmonary emphysema, as well as the skin, fibrotic and/or scalp pathologies or disorders, suggesting that its inhibition or stimulation may open therapeutic avenues [60]. For instance, it is well known that MMP-1 activity increases with age and that this increase, together with cell growth deceleration, contributes to chronologic skin aging [61]. Similarly, smokers' skin also has a premature aging aspect in which MMP-1 is overexpressed [62]. It should be pointed that the level of MMP-1 expression can be influenced by different single-nucleotide polymorphisms (SNPs) in the promoter region. A functional polymorphism at position -1607 has been shown to alter the transcriptional activity of MMP-1 and was associated with diverse pathological processes [63].

MMP-7

MMP-7 (matrilysin), produced uniquely in epithelia, may act on growth factors and matrix proteins and in the stomach is increased with *Helicobacter pylori* (*H. pylori*) infection. *H. pylori* is a well recognized gastric carcinogen, and MMP-7 is commonly upregulated in gastric carcinoid cancer [64, 65]. It has been shown that MMP-7 acts as an epithelial-derived signal increasing the bioavailability of insulin-like growth factor-II (IGF-II) released from myofibroblasts in the microenvironment surrounding the tumor, where various kinds of IGF/IGFBP (insulin-like growth factor binding proteins) complexes are found, thereby favoring cancer cell growth and survival during the processes of invasion and metastasis [66]. Another result from Varro *et al.* also validated that stimulation of gastric MMP-7 by elevated plasma gastrin may activate epithelial-mesenchymal signaling pathways regulating myofibroblast function via the mitogen-activated protein kinases (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways and contribute to stromal deposition in enterochromaffin-like (ECL) cell carcinoid tumors [67]. On the basis of these findings, effective inhibitors of MMP-7 might be hopeful for the treatment of *H. pylori* infected gastric cancer.

MMP-3

MMP-3 (stromelysin-1) is proposed to play important roles in both physiological and pathological tissue remodeling processes such as tumor angiogenesis, pulp wound healing, and bone resorption during orthodontic tooth movement [68]. For example, to investigate the function of certain MMPs during pulp wound healing, Zheng *et al*. provided suggestive evidence by establishing a rat dental pulp injury model that MMP-3 released from endothelial cells and/or endothelial progenitor cells in injured pulp, which plays critical roles in angiogenesis and pulp wound healing. Additionally, MMP-3 enhanced proliferation, migration, and survival of human umbilical vein endothelial cells *in vitro* [69]. In another study to compare MMP-3 expression by oral and skin fibroblasts and investigate a role for MMP-3 in mediating collagen gel contraction, the results provide suggestive evidence that increased MMP-3 production by oral fibroblasts may underlie the differences in wound-healing outcome seen in skin and oral mucosa [70].

It should be noticed that there are diverse types of MMPs that differ structural and functionally, hence, we can not mention them one by one. This article relates only to those whose functions are especially mentioned in recent MMPI-related patents (2005-2010). Furthermore, given MMPs are a family of structural and functional related endopeptidases, therefore in many cases, certain disease (e.g. tumor invasion, angiogenesis and building of metastatic formations) might be related to diverse MMP members. A good example is a variety of MMP members (MMP-1, -2, -8, -9, -10, -11, -12, -13, -15, -19, -23, -24, -27 and -28) have been proved to be associated with breast cancer development and tumor progression [71]. More recently, studies from Hawinkels *et al.* display that MMP-14 mediates endoglin shedding, which may regulate the angiogenic potential of endothelial cells in the tumor microenvironment [72]. The inhibitors of MMP-13, MMP-14 or MMP-1 are, therefore, might be used in the inhibition of metastasis, invasion or proliferation of various tumor cells [73]. Besides, MMP-1, -2, -9 and -13 have been found to be elevated in the tissues and body fluids surrounding damaged tissues. As a result, these subtypes often have a role in cardiovascular diseases in that they are believed to be involved in atherosclerotic plaque rupture, aneurysm and vascular and myocardial tissue morphogenesis, etc. [74, 75].

In addition, the profile of MMP expression has been shown to be modified by both matrix composition and exogenous growth factors, suggesting a major collective role of different MMP members. For example, the angiogenic basic fibroblast growth factor (bFGF) upregulates the expression of the gelatinases (MMP-2 and -9), the stromelysins (MMP-3, MMP-10 and MMP-11) and the interstitial MMP-13, whereas vascular endothelial growth factor (VEGF) leading to a marked increase in expression of MMP-2 only [76].

MMP-8

MMP-8 (collagenase-2; neutrophil collagenase), which is produced by neutrophils, has been recognized, in most cases, as a cancer anti-target with protective or beneficial functions based on its ability to regulate the inflammatory response induced by carcinogens. For instance, to dig out the putative anti-metastatic potential of MMP-8 in both mice and human, results from Gutiérrez-Fernández *et al*. displayed that MMP-8 has the ability to reduce metastasis formation by modulating malignant cell adhesion and invasion [77]. Knock-out of MMP-8 is also correlated with significantly improved skin tumor susceptibility in male mice [78]. Consistent with these studies, further investigations have revealed that the protective function of MMP-8 is more likely linked to its proteolytic manipulation of inflammatory mediators rather than to its traditional function as a collagenase participated in the degradation of fibrillar collagens [79]. Moreover, MMP-8 can be a central mediator in chronic periodontitis by the cooperative action of other MMPs (e.g. MMP-14), reactive oxygen species, and microbial proteases [80]. These data indicate that MMP-8 may participate in wound repair, chronic periodontitis as well as tumor protection, opening the possibility to develop new strategies for treating corresponding defects.

MMP-25

MMP-25 (leukolysin, membrane type-6 MMP or MT6-MMP), which is released mainly by granulocytic cells, primarily neutrophils, is a novel identified MMP subtype. Evidence revealed that it might be a potential serum marker for chronic airways inflammation, such as atopic asthma and COPD [81]. Recent data also suggested that MMP-25, especially because of its restricted cell/tissue expression pattern and cell surface/lipid raft localization, plays an essential role in MS pathology [82], and chronic or aggressive periodontitis as well [83, 84].

UPDATED MMPI-RELATED PATENTS

To conquer the challengeable issue in MMPI research, the primary goal of current registered patents regarding MMPs is to provide potent inhibitors with selectivity profiles of individual MMPs. In consequence, the fulfillment of a wide program of patented synthetic or natural products led to potential MMPIs with high selectivity and reduced side effects, providing new hope for MMPI development for both chronic and acute diseases. For clarity, not all MMPI-related patents are enumerated, only noteworthy compounds with breakthrough, either in chemical structures or selectivity on MMP inhibition, are described (see Table **1**) [85-154]. Additionally, these patents are sorted by year (2005-2011), with an emphasis on the illustration of structural characteristics and/or potential pharmaceutically application. And else, we are particularly concerned about are those compounds that might be potential leads to be further developed into drug candidates, which have been marked with an asterisk. From the brief description of the patented MMPIs, we can see that recent published patent targeting the MMPs covers a library of structurally diverse compounds which might be used in the prevention, control, or treatment of certain MMP-mediated disorders such as arthritis and cancer.

From the perspective of the target MMPs, in the endeavor to find selective and potent compounds against a MMP of interest, considerable efforts are made on the exploitation of innovative compounds targeting MMP-13, while MMP-12 and gelatinases (MMP-2 & -9) are in the next place, followed by MMP-3, MMP-1, and MMP-7, whose physiological roles are found to be closely related to arthritis, chronic respiratory diseases and cancer and so on.

In addition, an array of molecules claimed to be derived from FBDD approach has presented hereby. These potential pharmacophore and the like should be considered as valuable hints for lead discovery and optimization or rational design of potent compounds. For example, a handful of sulfonamide- or sulfone-derived MMPIs claimed recently exhibited potent MMP inhibitory activities or enhanced selectivity. For clarity, a dotted box outlines the common sulfonamide- or sulfone-containing structural motif, which has been widely employed for the discovery of biologically active molecules with pharmacological applications. This is because when this highly polarized sulfonamide fragment, which is similar with the structurally related sulfamide or sulfamate motif, incorporates into other drug-like molecules, the produced molecular scaffolds tend to exhibit improved efficiency and/or physicochemical profiles, in terms of enhanced water solubility, favorable bioavailability, low cytotoxicity, etc., offering a wide opportunity for novel drug discovery [155, 156].

Over the past decade, a vast number of literature have disclosed that the sulfonamide or sulfone functionality plays an important role in MMP inhibition via the extensive SAR studies as well as x-ray crystallography data [157-162]. It revealed that the sulfonamide or sulfone group was incorporated in the inhibitor to improve the enzyme-inhibitor binding affinity, not only by forming extensive hydrogen bonding with the enzyme backbone but also by properly accommodating the orientation of the hydrophobic substituents into the key binding pocket of MMPs (e.g. S_1' or S_1 pocket) and enabling it to plunge in deeply [163, 164]. It is worth mentioning that many sulfonamide- or sulfone-derived inhibitors have been used in clinical trials for the treatment of various cancers or chronic heart failure, such as CGS-27023A, AG3340 (Prinomastat), CP471358, PG-530742 and RS130830 as well (see Fig. (**2**)) [165-168]. Another representative sulfone-containing case is Abbott's **ABT-518**, a potent retrohydroxamate MMPI, demonstrates more than 200-fold MMP-9 inhibitory potency in contrast to its ether-containing counterpart **ABT-770** (see Fig. (**3**)) in pre-clinical models [169, 170].

Another interesting fragment with drug-like potential amongst these patented MMPIs is the hydantoin scaffold, which should also be considered for future MMPI design. A number of hydantoin derivatives have been reported to demonstrate various pharmacological activities. Two representative MMPIs, **BMS-275291** and **Trocade®/Ro 32-3555**, which are used as VEGF inhibitor cartilage protective agent (CPA), have been actually used in clinical for the treatment of NSCLC and RA, respectively (see Fig. (**4**)) [171, 172].

When it comes to ZBGs amongst these issued MMPI-related patents, classical hydroxamic acid and carboxylic acid are still commonly used on the premise of achieving selective MMP inhibition or improved efficacy across an

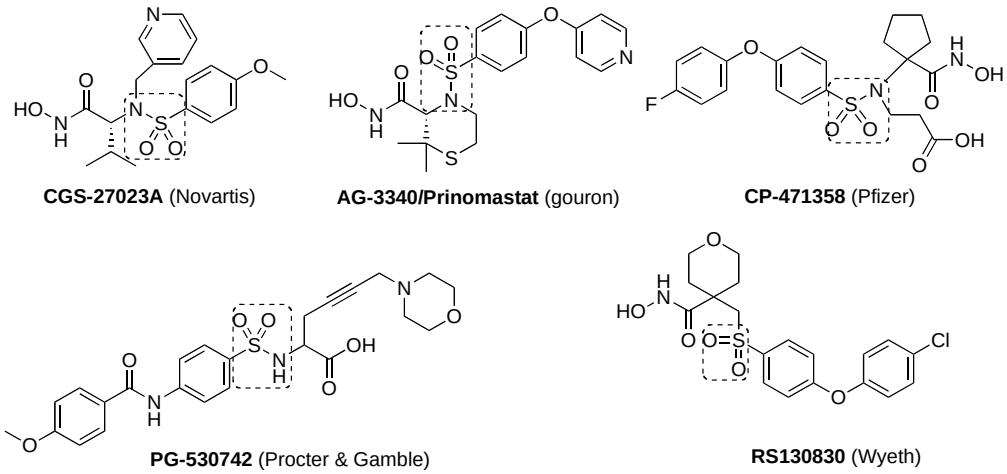


Fig. (2). Representative Sulfonamide-Based MMPIs in Clinical Usage (A Dotted Box Outlines the Common Sulfonamide or Sulfone Structural Features).

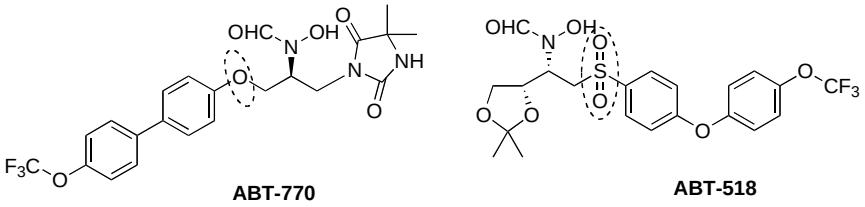


Fig. (3). Chemical Structures of ABT-770 and ABT-518. (The Dotted Area Shows that the Replacement of the Ether Linkage Of ABT-770 with a Sulfone Moiety Resulted in a Substantial Increase in MMP-9 Inhibition).

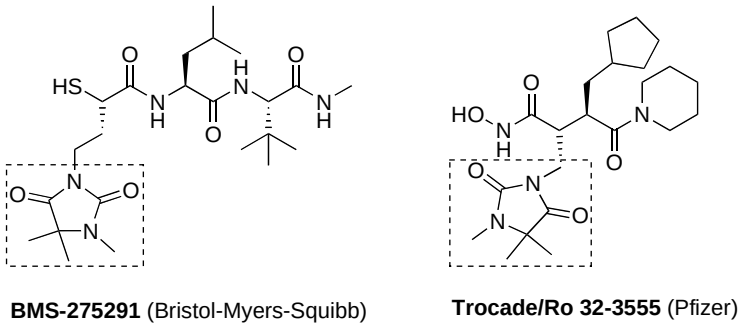


Fig. (4). Chemical Structures of BMS-275291 and Trocade with the Common Drug-Like Hydantoin Scaffold.

array of unwanted side effects. As aforementioned, MMPIs with the hydroxamate or carboxylic acid as ZBGs can still achieve favorable strength and great potentials provided by a careful selection of chemical backbone as well as the incorporation of optimized extensions targeting both side of the active site (also called as double-hand inhibitors). Furthermore, it is no doubt that new ZBGs development and also the devoid of ZBG is the new trend in MMPI research field, as can be seen in Table **1**.

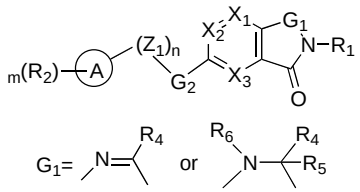
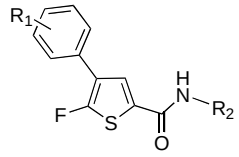
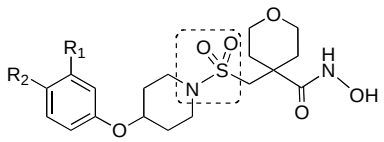
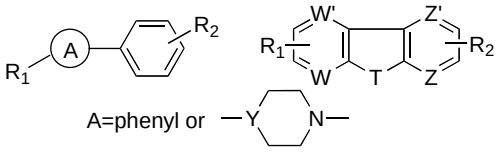
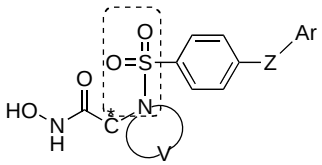
CURRENT & FUTURE DEVELOPMENTS

Key Findings and Weakness in the Research of MMPI

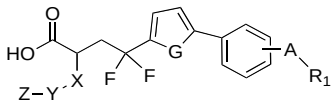
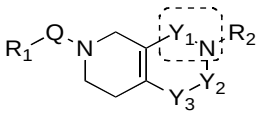
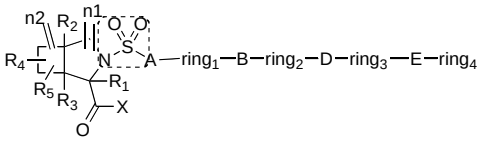
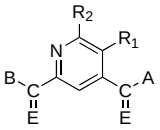
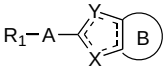
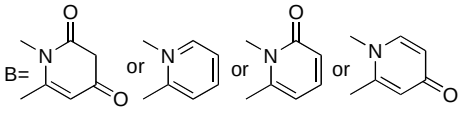
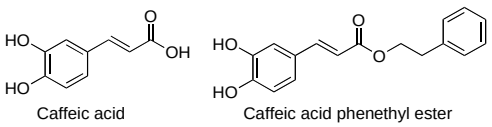
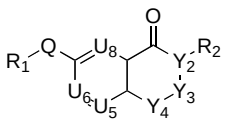
In view of the involvement of MMPs family members in a wide variety of physiological and pathological conditions, especially skeletal growth and remodeling, wound healing, MS, cancer and arthritis, natural or synthetic inhibitors endowed with adequate pharmacological and selectivity profile by targeting at these enzymes are therefore amenable to therapeutic intervention, offering hopeful perspectives for future drug exploration.

Theoretically speaking, endogenous specific TIMPs can be exploited to combat these pathological states and some of them have been practically tested in animal experiments with successfully therapeutic results [173]. However, they are of limited clinical usage owing to inadequate pharmacological stability. In specific, TIMPs are usually macromolecular proteins which cannot be easily penetrate the tissue barriers and administered systemically on a long-term basis. Moreo-

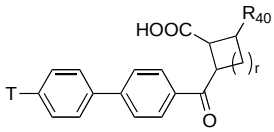
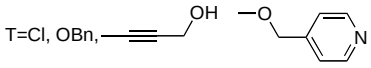
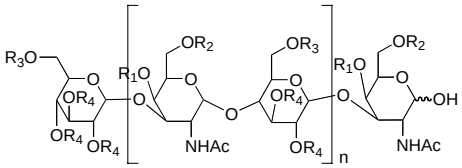
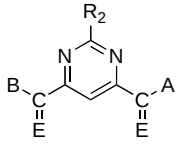
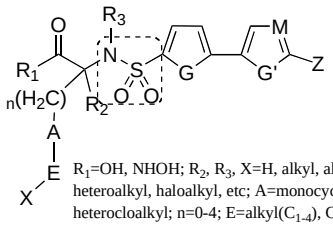
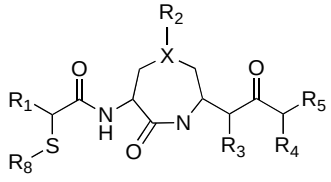
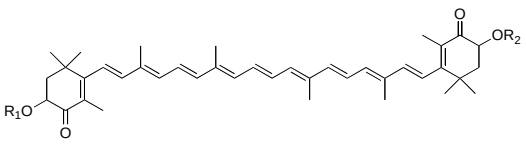
Table 1. Representative Issued Patented MMPIs from 2005 to 2011.

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Jan.6, 2005	US20050004177	 X_1--X_3=N, CR_3; R_3=H, alkyl(C_{1-6}), NH_2, mono(C_{1-6})alkylamino, di(C_{1-6})alkylamino, hydroxyl, (C_{1-6})alkoxy, halogen. R_4,R_5=alkyl(C_{1-6}), aryl, arylalkyl(C_{1-6}), cycloalkyl, heteroaryl, etc; R_6=H, CF_3, OR_7,NR_7R_8; R_7,R_8=H,alkyl(C_{1-6}). G_2 represents C≡C, -CH=C=CH-, C=S etc. Z_1=CR_9R_{10}; R_1, R_2= alkyl(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), etc.	This invention claims bicyclic-based heterocyclic compounds as allosteric inhibitors of MMP-13 and alpha-2-delta receptors including gabapentin and pregabalin.	[85]
Jan.13, 2005	WO2005003114	 (I) R_1=halo(C_{1-6})alkoxy, (C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, phenyl, cyclohexyl, heterocycle, etc; R_2=-U-R_4; U=a linear (C_{1-4})alkylene chain optionally substituted with a group selected from carboxyl, carboxy(C_{1-6})alkyl, (C_{1-6}) alkyloxycarbonyl and (C_{1-6})alkyloxycarbonyl(C_{1-6})alkyl, etc; R_4=phenyl, cyclohexyl, morpholin-4-yl, etc.	The invention claims 5-fluoro-4-phenyl-2- thiophenecarboxamide derivatives (I) that can be used as MMP-12 inhibitors and, to a lesser extent, MMP-13 inhibitors.	[86]
Jan.19, 2005	CN1568320	 R_1, R_2=optionally selected from H, CF_3, CF_2H, CFH_2, which may be the same or different.	The invention relates to a number of hydroxamic acid containing sulfonamide-based compounds that can be used as potent MMPIs for treatment pathologic conditions or disorders mediated wholly or in part by MMPs. Moreover, they advantageously do not cause tendonitis in a relevant animal model, expecting to be of use in medicine, especially where the avoidance of side effects such as joint pain is desired.	[87]*
Jan.27, 2005	US20050020607	 Y=CH or N; R_1=alkyl, aryl halo, amino, substituted and disubstituted amino, alkoxy. R_2=carboxyalkyl ketone or oxime, a carboxyalkyl sulfonamide. T=O, CH_2, SO, SO_2, C=O, NR_3, NR_3C=O. W, W', Z, Z' are each the same or different and each is CR_3. R_3=alkyl, halo, alkoxy, acyl, aryl.	The invention provides substituted bicyclic or tricyclic MMPIs which can be MMPIs used for treating and preventing vascular diseases such as peripheral vascular disease, coronary heart disease, stroke as well as restenosis.	[88]
Feb.1, 2005	US6849732	 Z=O, S; V is a divalent radical which together with C* and N forms a six-membered ring; Ar=aryl or heteroaryl group.	The invention relates to sulfonamide-based compounds that inhibit metalloproteinases, particularly MMPs and tumor necrosis factor-α convertase (TACE).	[89]*

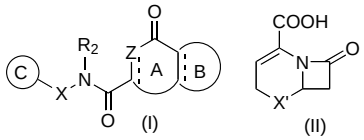
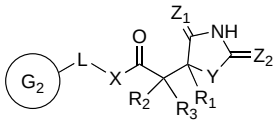
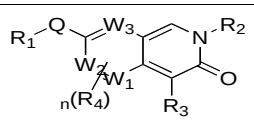
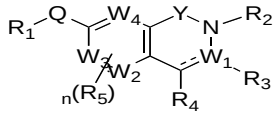
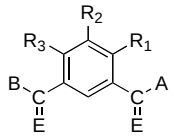
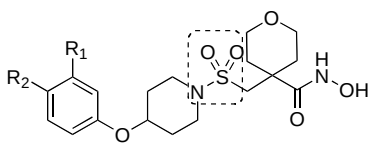
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Feb.8, 2005	US6852751	 A=a covalent bond, alkyl(C_{1-3}), O, S, SO, SO_2; R_1, Z=OH, alkoxy, halogen, CN, alkyl, alkenyl, alkyne, heteroalkyl, aryl ,etc; X=a covalent bond, alkyl(C_{1-3}),etc; Y=a covalent bond, O, S, SO, SO_2, NR_2; G=S, O, NR_3, CH=CH.	The provided carboxylic acid containing compounds are potent inhibitors of MMPs which are effective in treating ailments characterized by excess activity of the unwanted MMPs.	[90]
Mar.22, 2005	US6869958	 R_1=C_5 or C_6 cycloalkyl-(C_{1-8} alkylenyl), etc; R_2=H, alkyl(C_{1-6}), phenyl-(C_{1-8} alkylenyl), etc; Y_1=CH_2, CO, SO_2, Y_2= CO, Y_3=NR_4, etc; R_4=H, CH_3, CH_3O, OH, CF_3, CN, Q=OCO, CHR_5CO, $OCNR_5$, NR_5CO, SCO, etc.R_5=H, alkyl(C_{1-6}), benzyl, etc.	The fused tetrahydropyridine derivatives can be potent MMPIs, showing especially excellent MMP-13 inhibitory activities.	[91]*
Apr.14, 2005	US20050080	 A=alkylene(C_{0-4}); B,D,E=alkylene(C_{0-4}), -B1-B2-B3-; B1=$(CH_2)_n$; B3=$(CH_2)_m$; m, n=0,1,2; B2=CO, alkenylene(C_{2-4}), NHCOO, SO_2NR_6, $OCONR_6$, etc; ring1--ring4=covalent bond, aryl(C_{6-14}), 4- to 15- membered Het ring; ring 4=aryl(C_{6-14}).	The invention relates to novel derivatives of saturated bicyclic imino acid derivatives, such as, in particular, decahydroisoquinoline-1-carboxylic acid, as effective and potent inhibitors of MMP-2, -3, -8, -9 and -13 while only having a weak inhibitory effect against MMP-1.	[92]
Apr.19, 2005	US6881743	 R_1,R_2=OH, halo, H, alkyl(C_{1-6}), alkoxy(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), NO_2, CN, CF_3, NR_4R_5; E=O, S; A, B=OR_4, NR_4R_5; R_4,R_5=H, alkyl(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), $(CH_2)_n$aryl, etc; n=0-6.	The pyridine derivatives can selectively inhibit MMP-13, displaying at least ≥10 times more potent versus MMP-13 than versus at least one of any other MMPs or TACE. As a result, they are especially useful for the treatment of multiple sclerosis.	[93]
May.24, 2005	US6897223	 A=NR(CO), (CO)NR, alkynyl(C_{2-6}), OC=O, OCNR, SC=O, NRC=S, etc; X, Y=N, NR_9, O, S, CR_{10}, etc; 	The mentioned pyridine fused bicyclic derivatives display differential metalloprotease activity (preferably MMP-13 inhibition). Additionally, they possess selectivity over a related group of enzymes known as reprolysins, such as TACE and aggrecanase.	[94]
Jun.16, 2005	WO2005053671	 Caffeic acid Caffeic acid phenethyl ester	The present invention relates to an MMP-9 inhibitor which contains caffeic acid (CA) or caffeic acid phenethyl ester (CAPE).	[95]
Jun.21, 2005	US6908917	 R_1=C_5 or C_6 cycloalkyl-(C_{1-8} alkylenyl), etc; R_2=H, alkyl(C_{1-6}), phenyl-(C_{1-8} alkylenyl), etc; Y_2=N, Y_3=CH_2, etc; Y_4=O, NR_5, R_5=H, alkyl(C_{1-6}); U_5, U_6, U_8=CR_4, N; R_3,R_4=H, F, Cl, CH_3, CH_3O, etc;	The invention relates to a chromone derived compounds are used as potent MMPIs, especially MMP-13 inhibitors.	[96]

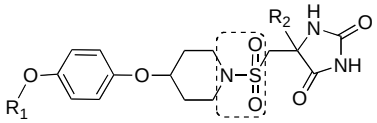
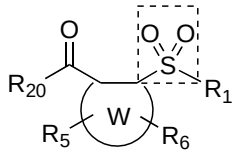
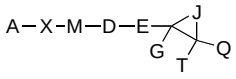
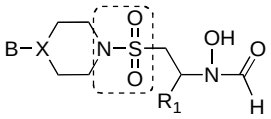
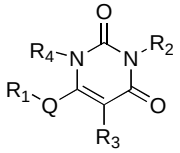
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Jun.28, 2005	US6911449	 r=0-2; R_{40}=a mono- or bi-heterocyclic structure.  T=Cl, OBn,	The invention claims novel substituted biaryl oxobutyric acid compounds or derivatives that are useful for inhibiting MMPs. Accordingly they can combat conditions to which MMP's contribute. Moreover, they might be useful tools for investigating functions and mechanisms of action of MMPs in both in *vitro* and *in vivo* systems.	[97]
Jul.7, 2005	WO2005061551	 (I) R_1, R_2, R_3 and R_4 represent H or SO_3M, n is an integer of between 0 and 200 and M is an alkali metal.	The invention relates to a kind of carboxy-reduced and chemoselectively *O*-sulphated derivatives of chondroitin sulphate having formula (I) which can be used as at least one of the inhibitors of MMPs such as MMP-7 and -2.	[98]
Aug.30, 2005	US6936616	 R_2=OH, halo, H, alkyl(C_{1-6}), alkoxy(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), NO_2, CN, CF_3, NR_4R_5; E=O, S; A, B=OR_4, NR_4R_5; R_4,R_5=H, alkyl(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), $(CH_2)_n$aryl, etc; n=0-6.	The pyrimidine derivatives or analogs can selectively inhibit MMP-13, with IC_{50} values typically in the range of from about 0.001 to 10 micromolar.	[99]
Sep.27, 2005	US6949545	 R_1=OH, NHOH; R_2, R_3, X=H, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, etc; A=monocyclic heterocloalkyl; n=0-4; E=alkyl(C_{1-4}), C=O, COO, $CONR_4$, SO_2, $CSNR_4$, etc; G, G'=S, O, NR_5, N=N, etc; M=CH, N; Z=$(CR_1R_7)_a$, LR_8, etc. a=0-4.	The related heterocyclic side chain containing, *N*-substituted compounds are effective in treating conditions mediated by excess activity of unwanted MMPs or elevated activity by MMPs. Of these MMPIs, carboxylic acid and hydroximic acid are used as ZBGs.	[100]*
Oct.11, 2005	US6953788	 R_1=alkyl(C_{1-6}), W-$(CH_2)_m$, etc; W=phthalimido, R_2=alkyl(C_{1-4}), $(CH_2)_p$-(C_{3-9})heteroaryl, etc; R_3=H, alkyl(C_{1-6}), $CH_2SCH_2NHCOCH_3$, etc; R_4=H, $(CH_2)_m$-$S(O)_pX'(R_6)_2$; R_5=H, alkyl(C_{1-6}), etc; R_8=H, COR_7, etc.	The invention claims certain novel 3-mercaptoacetylamino- 1,5-substituted-2-oxo-azepan derivatives useful as inhibitors of MMPs, which demonstrate obviously advantageous to control the imbalance of unwanted MMPs without generating carcinogenic side-products.	[101]
Oct.17, 2005	JP2006008714	 R_1 and R_2 represent saturated or unsaturated fatty acids.	The invention provides compounds with saturated or unsaturated fatty acids structure for inhibiting MMP.	[102]

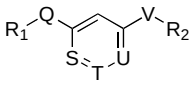
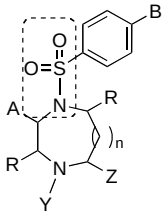
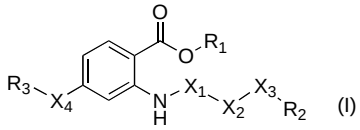
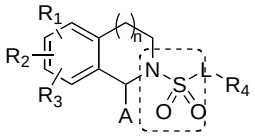
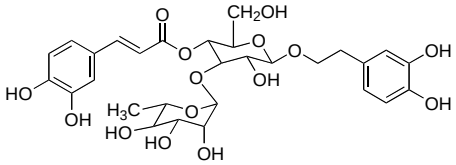
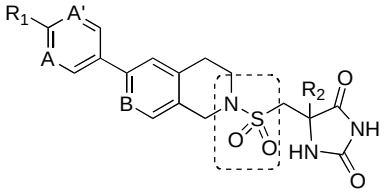
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Nov.10, 2005	WO2005105760	 (I) (II) Ring A=optionally substituted *N*-containing heterocycle, ring B, C=monocyclic homocycle, etc. Z=N, NR_1; R_1, R_2=H, substituted hydrocarbon, ----is a single or double bond; X=optionally substituted spacer having 1~6 atoms, X'=S, O, SO, CH_2.	The invention provides novel heterocyclic amide derivatives having a superior MMP inhibitory activity (especially the MMP-13 activity) and use as a drug for the prophylaxis or treatment of MMP-13 related diseases such as osteoarthritis, rheumatoid arthritis and so on.	[103]
Dec.3, 2005	US2005245586A1	 X=O, CH_2, NR_4; Y=NH, *N*-methyl; Z_1, Z_2=O, S; R_1=H, alkyl(C_{1-6}), saturated or unsaturated 3-10 membered ring system which comprise at least one ring heteroatom (N, O, S), etc. R_2, R_3=H, alkyl(C_{1-6}); L=CH_2CO, $COCH_2$, alkenyl(C_{2-6}), alkynyl(C_{1-6}), etc. G_2=saturated or unsaturated 3-10 membered ring system which comprise at least one ring heteroatom (N, O, S), the ring can be optionally substituted with at least one substituent selected from halogen, OH, CN, NO_2, alkyl(C_{1-6}), etc.	The invention provides a class of 2,5-dioxoimidazolidin-4-yl acetamines analogues that can be used as specific MMP-12 inhibitors.	[104]*
Dec.13, 2005	US6974822	 R_1=C_5 or C_6 cycloalkyl-(C_{1-8} alkylenyl), etc; R_2=H, alkyl(C_{1-6}), phenyl-(C_{1-8} alkylenyl), etc; R_3=H, alkyl(C_{1-6}), alkynyl(C_{2-6}), alkenyl(C_{2-6}),cycloalkyl(C_{3-6}), etc; R_4=H, alkyl(C_{1-6}), NH_2, OH, halo; n=0-3; Q=OCO, CHR_5CO, $OCNR_5$, etc. W_1--W_3=N, CR_4.	The invention offers a group of MMPIs characterized as being 3-isoquinolinone derivatives, which are especially useful as MMP-13 inhibitors.	[105]
Dec.20, 2005	US6977261	 R_1=C_5 or C_6 cycloalkyl-(C_{1-8} alkylenyl), etc; R_2=H, alkyl(C_{1-6}), phenyl-(C_{1-8} alkylenyl), etc; R_3, R_4=H, alkyl(C_{1-6}), alkynyl(C_{2-6}), alkenyl(C_{2-6}),cycloalkyl(C_{3-6}), etc; R_5=H, alkyl(C_{1-6}), NH_2, OH, halo; n=0-3; Q=OCO, CHR_6CO, $OCNR_6$, etc. W_1--W_3=N, CR_5, CHR_5.	The MMPIs are characterized as being azaisoquinoline derivatives, which are especially useful as MMP-13 inhibitors.	[106]*
Feb.7, 2006	US6995151	 R_1, R_2, R_3=H, halo, OH, alkyl(C_{1-6}), alkoxy(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), NO_2, CN, CF_3, NR_4R_5; E=O, S; A, B=OR_4, NR_4R_5; R_4, R_5=H, alkyl(C_{1-6}), alkenyl(C_{2-6}), $(CH_2)_n$aryl, $(CH_2)_n$cycloalkyl, etc, n=0-6.	The related isophthalic acid derivatives or analogs show enzymatic inhibition against MMPs, especially MMP-13.	[107]
Mar.21, 2006	US7015234	 R_1, R_2=H, CF_3, CF_2H, CFH_2, etc.	The hydroxamic acid-containing sulfonamide derivatives are potent MMPIs which advantageously do not cause tendonitis in a relevant animal model. Accordingly, they might be expected to be drugable leads in medicine, especially where the avoidance of side effects, such as dose-limiting joint pain, MSS, is desired.	[108]*

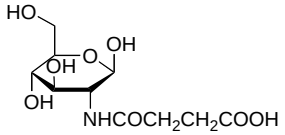
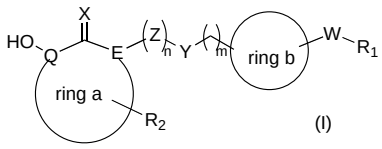
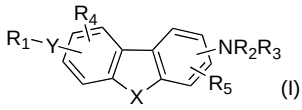
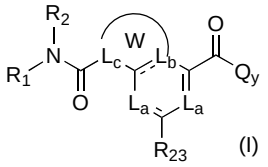
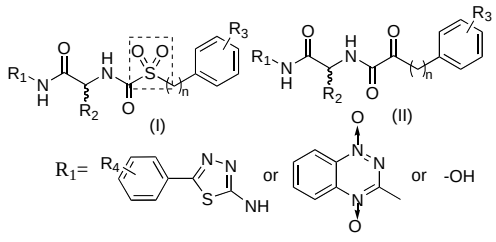
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Jun.22, 2006	WO2006064218	 R_1=alkyl($C_{2\text{-}4}$) and is substituted by two or more fluorine groups; R_2=CH_3, C_2H_5.	The invention provides a new class of hydantoin derivatives that are inhibitors of metalloproteinases and are of particular interest in inhibiting MMP-13 (collagenase 3).	[109]*
Oct.3, 2006	US7115632	 W=a 5- or 6-membered aromatic or heteroaromatic ring; R_1=a substituent containing a 5- or 6-membered cyclohydrocarbyl, heterocyclo, aryl, etc; R_5, R_6=hydrido, alkyl, cycloalkyl, acylalkyl, halo, etc; R_{20}=OR_{21}, $NR_{13}OR_{22}$, etc.	In accordance with the present invention, the mentioned aromatic sulfonyl aryl or heteroaryl or sulfonyl α-cycloamino hydroxamic acid (hydroxamates) derivatives display particular inhibitory activities towards one or more of MMP-2, -9 or -13, while generally exhibiting a limited or minimal effect against MMP-1. They are believed to be associated with diseased conditions or otherwise pathological breakdown of connective tissue without excessive inhibition of other collagenases essential to normal bodily function such as tissue turnover and repair.	[110]
Dec.5, 2006	US7144917	 A−X−M is a hydrophobic group; D=O, S, alkyl($C_{1\text{-}6}$), a direct bond, SO, SO_2, CO, NR, COO, NRCO, OCO; E=alkyl($C_{1\text{-}6}$), a direct bond,cycloalkyl($C_{3\text{-}8}$), alkenyl(C2-6), etc; J=O, S; J, T, Q=H, alkyl($C_{1\text{-}6}$), cyano.	The 3-membered ring-containing compounds are mechanism- based MMPIs, in which the relatively non-polar and hydrophobic aryl moiety (A-X-M) can fit in the deep S_1' pocket and has a favorable interaction with the enzyme. The heteroatom (e.g. thiirane) can coordinate with the active zinc ion, and second optional group (e.g. esters or amides) can bind with one or more subsites in the enzyme. All these ensure the MMPIs preferable.	[111]
Dec.21, 2006	US20060287338	 B=3- or 4-monosubstituted phenyl group (halogen or CF_3), etc; X=C or N; R_1=trimethyl-1-hydantoin C_2-4alkyl, phenyl, phenylSO_2NHC_2-4alkyl, 2-pyridyl, etc.	The invention claims new sulfonamide-containing hydantoin derived compounds which might have different degrees of potency and selectivity for inhibiting various metalloproteinases, in particular the MMP-13, as well as MMP-9.	[112]*
Jan.9, 2007	US7160893	 R_1=C_5 or C_6 cycloalkyl-($C_{1\text{-}8}$alkylenyl), 8- to 10-membered heterobicycloalkyl($C_{1\text{-}8}$alkylenyl)$_m$, etc; R_2=H, alkyl($C_{1\text{-}6}$), phenyl-($C_{1\text{-}8}$alkylenyl)$_m$, etc; R_3=H, CH_3, CH_3O, $CH=CH_2$, OH, CF_3, CN, HC=O, NH_2, H_2NC=O, halo, COOH, etc; Q=O, S, SO, SO_2, NR_5; R_4, R_5=H, alkyl($C_{1\text{-}6}$), etc.	The invention provides a group of selective and allosteric MMP-13 inhibitors having an anti-arthritic effect characterized as being pyrimidine-2,4-dione derivatives. Therefore, they can inhibit, prevent, or reverse the progression, in part or in whole, of any one or more symptoms of the arthritic diseases and disorders.	[113]

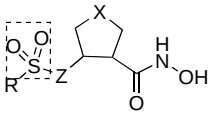
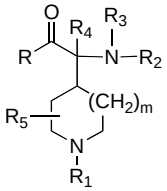
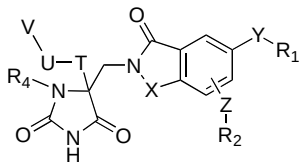
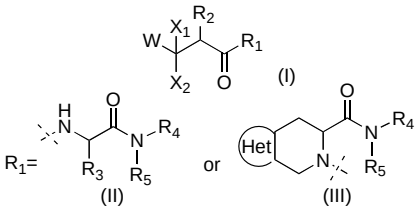
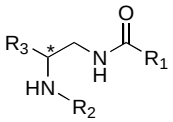
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Feb.20, 2007	US7179822	 R_1, R_2=H, alkyl(C_{1-6}),alkenyl(C_{2-6}), alkynyl(C_{2-6}), cycloalkyl(C_{3-6}), phenyl-(C_{1-6}alkylenyl), etc; S, T, U=CR_4, etc; V=5-membered heteroarylenyl; Q=OCH_2, NR_6CH_2, OCO, $OCNR_6$, etc.	The invention claims a group of selective MMP-13 inhibitors characterized as being hetero biaryl derivatives.	[114]*
May.29, 2007	US7223751	 n=0-3; A=COOH, CONHOH, CH_2SH, CH_2OH; B=H, alkyl(C_{1-18}), NO_2, aryl, heteroaryl, pyrrole, halo, O-aryl, etc; R=H, alkyl(C_{1-8}), aryl, heteroaryl, etc; Z=H, =O, =S; Y=H, alkyl(C_{1-8}), aryl, heteroaryl, etc.	The invention concerns a kind of novel sulfonamide-based 7-membered heterocyclic compounds substituted with a phenyl sulfonyl group at the 4-position, acting as superior angiogenesis controlling to inhibit overexpression of MMPs.	[115]*
Aug.22, 2007	EP1820795	 (I) R_1=H, carboxy-protecting group; R_2=substituted phenyl, heterocyclic group; R_3=substituted phenyl, monocyclic heterocyclic group; X_1=carbonyl, etc; X_2, X_6=substituted alkylene group, a bond; X_3, X_5=O, S, a bond; X_4= -X_5-X_6-, -X_6-X_5-.	The invention provides a novel anthranilic acid derivative having the selectively inhibitory activity of MMP-13.	[116]*
Aug.30, 2007	US20070203118	 R_1--R_3=H, halo, NO_2, CN, OH, alkyl(C_{1-6}), alkenyl(C_{2-6}), cycloalkyl(C_{3-8}), etc; n=0,1,2; L=O, -NR_{14}, a covalent bond or -$(CH_2)_q$, R_{14}=H, (C_{1-6})alkyl, q=1,2,3,4; R_4=phenyl, (C_{5-14})heteroaryl, etc. A= CH_2SH, C(O)OH, C(O)NHOH, C(O)R_5, etc.	The invention provides sulfonamide-containing tetrahydroisoquinolines which might be used as effective MMPIs.	[117]*
Sep.14, 2007	JP2009067749		The invention provides the phenol compound derived from natural products, namely *Osmanthus fragrans var. aurantiacus*, showing MMP-1, -2 inhibitory activity, estrogen-like activity, profilaggrin production-promoting activity, filaggrin production-promoting activity and cyclic AMP (cAMP) phosphodiesterase inhibitory activity, respectively.	[118]
Nov.28, 2007	CN101080403	 R_1=H, halogen, CF_3, CH_2CN; R_2=alkyl(C_{1-3}); A, A', B=CH, N.	The invention relates to novel hydantoin derivatives that are useful as MMPIs, particularly as potent MMP-12 and/or MMP-9 inhibitors.	[119]*

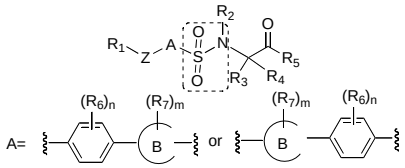
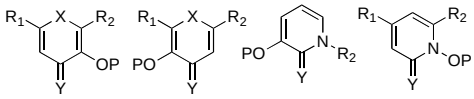
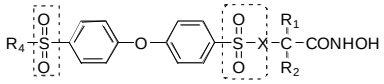
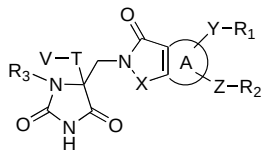
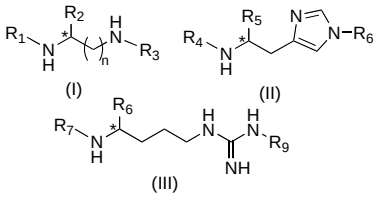
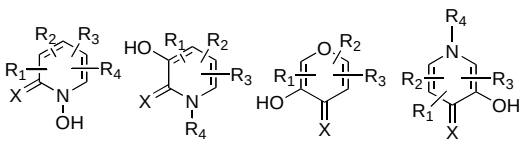
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Dec.27, 2007	WO2007148848		The invention relates to a carboxylated glucosamine (CGIc) compound (or containing the CGIc compound as an effective constituent) as MMP-9 inhibitor, which can be used for inhibiting the activation and expression MMP-9 in HT1080 (human fibrosacroma cells).	[120]
Apr.17, 2008	WO2008045668	 (I) ring a=heteroaryl, 6-, 7-, 8- or 9-membered heterocyclic ring; X=O, S; E,Q=sp^2 C or N; ring b=aryl, heteroaryl, etc; R_1, R_2=halo, CN, OH, SH, NH_2, alkenyl(C_{2-6}), alkyl(C_{1-10}), alkoxy, alkynyl(C_{2-6}), aryl, etc; W= $S(O)_p$, $(CH_2)_p$-O, CO, alkylidene(C_{1-3}), etc; p=0,1,2; Y=O, S, SO, SO_2, SO_2NR_6, etc; Z=CHR_{10}, $CHR_{10}CHR_{11}$; R_{10}, R_{11}=H, alkyl(C_{1-6}), aryl, alkenyl(C_{2-6}), alkyl(C_{2-6}), heteroaryl, etc; m=0,1,2; n=0,1.	This invention provides novel heterocyclic derived compounds as potent MMPIs (e.g. MMP-2,-9,-13) that are useful for treating disorders ameliorated by antagonizing MMPs. More specifically, they have utility in the treatment and prevention of strokes.	[121]
May.15, 2008	WO2008057254	 (I) R_1=N-linked COOH or COOH-protected, natural or non-natural amino acid, or an N-linked amino acid derivatives; R_2, R_3=H, oxo, OR_8, $COOR_8$; $C(S)OR_8$, etc; R_4,R_5=H, CN, NO_2, halo, OR_8, alkyl(C_{1-10}), etc. X=O, S, SO, SO_2, NR_6; Y= SO, SO_2, CO.	The invention relates to a class of tricyclic compounds, namely amino-substituted xanthene, thioxanthene and carbazole sulfonamido-carboxylic acid of carboxamido carboxylic acid derivatives that can be used to treat MMP-mediated conditions, and especially to inhibit MMP-12. Accordingly, they can be used for treatment of pathologic conditions or disorders mediated wholly or in part by MMPs, such as asthma and COPD.	[122]
May.29, 2008	WO2008063670	 (I) R_1=H, alkyl, haloalkyl, trifluoroalkyl, alkenyl, alkynyl, aryl, heterocycloalkyl, spiroalkyl, cycloalkyl, etc; R_2=H, alkyl, etc; R_{23}=H, OH, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, NO_2, CN, etc; L_a=CR_9, N; L_b=C, N, etc; L_c=C, N; Q_y=NR_1R_2, OR_1; W=5-or 6-membered ring.	The invention relates to a new class of heterobicyclic amide containing pharmaceutical agents that exhibit potent MMP-3 and/or MMP-13 inhibiting activity and/or activity toward MMP-8, MMP-12, ADAMTS-4, and ADAMTS-5 (ADAMTS, means a group of proteases). Besides, they demonstrate increased potency and selectivity in relation to currently known MMP-13 and/or MMP-3 inhibitors.	[123]
Oct.8, 2008	CN101279956	 (I) (II) R_1= R_2=H, alkyl(C_{1-5}), alkenyl(C_{1-5}); R_3=H, OH, OCH_3; R_4=H, F, Cl, Br, I, NO_2, CH_3, OCH_3; n=0-3.	The invention presents peptidomimetic MMPIs. Importantly, the synthetic route is relative short with high yields and the starting materials are easily available, which is suitable for the industrial production.	[124]

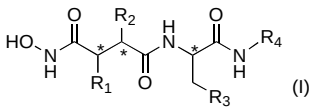
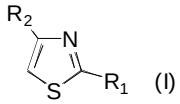
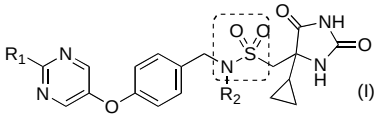
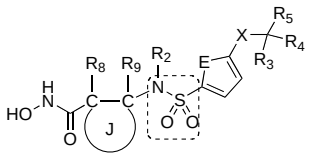
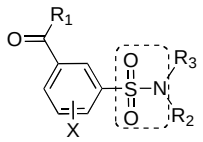
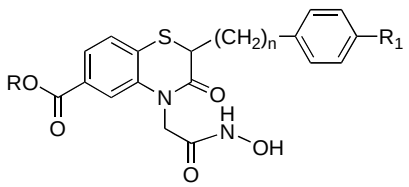
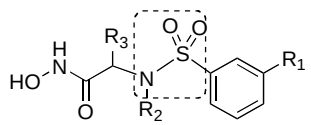
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Dec.18, 2008	US20080312329	 X=$(CH_2)_nO$, $(CH_2)_nS$, $(CH_2)_nNR_1$, $(CH_2)_n(CH_2)$, CH=CH; n=0,1,2; R,R_1=a substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, heteroaryl group, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl; Z=NH, CH_2.	The patent presents a group of compounds based on a 5-membered ring structure comprising a metal binding group, namely hydroxamate group, capable of binding the metal ion within the active site of the enzyme, and one sulfonyl functional groups as side chain, that can be used as inhibitors of all zinc-dependent MMPs, such as MMP-1, -3, -7, -8, -11, and -13, etc.	[125]
Jan.26, 2009	JP2009137997	 R=OH, NHOH; R_1=H, optionally substituted lower alkyl, aryl-lower alkyl; R_2= biarylsulfonyl, R_3=H, lower alkyl, R_4,R_5=H, lower alkyl, lower alkoxycarbonyl, m=0-3	The invention describes novel α-(azacycloalkyl)- substituted biaryl-sulfonamidoacetic acid derivatives which can be used to inhibit matrix degrading MMPs, such as gelatinases, stromelysin and collagenase, in particular, collagenase-3 (MMP-13).	[126]
Jan.27, 2009	US7482370	 X=S, $C(R_4)_2$, NR_4; T=H, alkyl, alkenyl, aryl, heteroaryl, cycloalkyl, etc; U=NR_4, O, NR_4CO, NR_4SO_2, $NR_4C{=}SNR_4$, NR_4CONR_4, etc; V=alkyl, aryl, heteroaryl, etc; Y, Z=NR_4, $CONR_4$, NR_4CO, O, S, CO, SO, SO_2, etc; R_1, R_2=H, OR_4, halo, alkyl, fluoroalkyl, aryl, etc; R_4=H, alkyl.	The invention claims novel hydantoin derivatives that can inhibit MMPs, ADAMs, TACE and/or prevent the release of tumor necrosis factor alpha (TNF-α). Inhibition of these enzymes can prevent the degradation of cartilage, thereby alleviating the pathological conditions such as OA and RA, respectively, as well as other auto-immune diseases. In accordance with these properties, they can be used as cartilage protecting therapeutics in the treatment of inflammatory disorders.	[127]*
Jan.29, 2009	WO2009012656	 R_3=natural or non-natural α-amino acids, R_2, R_4=alkyl(C_{1-6}), alkenyl(C_{1-6}), alkynyl(C_{1-6}), aryl(C_{1-6}), heterocycloalkyl(C_{1-6}), spiroalkyl, cycloalkyl(C_{3-8}), etc; R_5=H, alkyl(C_{1-6}). Het=aryl, heteroaryl, etc; W=CONHOH, COOH; X_1, X_2=H, halo, CN, NO_2.	The invention provides hydroxamic acid and carboxylic acid derivatives as effective MMPIs.	[128]
Feb.4, 2009	CN101357893	 R_1=aryl, heteroaryl, arylalkyl(C_{1-6}), organic acids, *N*-protected, natural or non-natural amino acid derivatives, etc; R_2,R_3=H, aryl, arylalkyl(C_{1-6}), arylalkenyl(C_{2-6}), etc.	The invention relates to ethylenediamine compounds that can be used as MMPIs for treatment pathologic disorders mediated wholly or in part by MMPs, such as inflammation, cancer, multiple sclerosis, ulcer, leukemia, asthma and COPD.	[129]

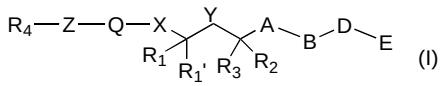
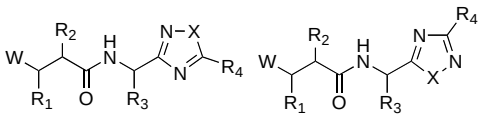
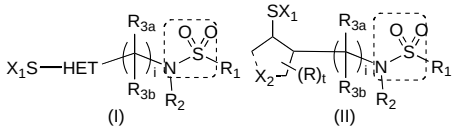
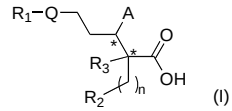
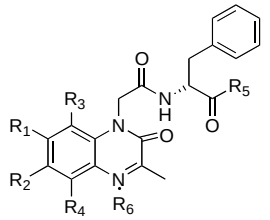
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Mar.12, 2009	US20090069304	 R_1=optionally substituted aryl; Z=alkylene ($C_{1\text{-}5}$), etc; R_6, R_7=halogen, lower alkyl; m, n= 0,1,2; R_2, R_3=H, lower alkyl; R_4=H; R_5= OH, lower alkyloxy, etc.	The invention claims novel sulfonamide derivatives exhibiting MMP-13 selective inhibitory activities.	[130]*
Mar.12, 2009	US20090068255	 X=O, NR'; R'=H, alkyl($C_{1\text{-}6}$), a nitrogen protecting group; Y=O, S; P=H, an oxygen protecting group; R_1=H, alkyl($C_{1\text{-}6}$); R_2= aryl- or heteroaryl-containing moiety which may be optionally substituted.	The invention relates to 6-membered herterocyclic MMPIs which are effective to improve the smoothness of skin, to prevent or reduce the appearance of wrinkles.	[131]
Mar.17, 2009	US7504537	 R_1, R_2 represent H, lower alkyl group, lower haloalkyl, etc; X represents methylene group or NR_3. R_3=H, lower alkyl group, etc. R_4=C1-4 lower alkyl group.	The present invention mentions hydroxamic acid derivatives which are proved to inhibit MMP-3 and/or MMP-13 selectively with reduced side effect.	[132]*
Apr.28, 2009	US7524842	 X=S, O, SO, SO_2, NR_3, $(C(R_3)_2)_m$; T=alkynyl; V=H, cycloalkyl, alkyl, aryl, heteroaryl, etc; Y, Z=NR_4, $CONR_4$, NR_4CO, O, S, CO, SO, SO_2, etc; m=1-3; R_1, R_2=H, CN, alkynyl, halo, alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl, etc; R_3=H, alkyl, aryl; R_4=H, alkyl, cycloalkyl, haloalkyl, OH, etc.	The invention provides a novel class of hydantoin derivatives as inhibitors of MMPs, ADAMs, TACE and/or TNF-α, which can be used in the treatment, prevention or amelioration of one or more of the symptoms of inflammation.	[133]*
Jul.15, 2009	CN101481325	 n=3, 4; R_1, R_3, R_4, R_6, R_7= heteroacyl, aryl, acyl, acylalkyl($C_{1\text{-}6}$), etc; R_2, R_5, R_8=CONHOH, COOH, $COCH_3$, $CONHNH_2$; R_9=NH_2-protected groups, such as NO_2, Boc, Fmoc, CPh_3, $COCH_3$, COC_2H_5, $COCF_3$, etc. * represents *S*-configuration	The invention relates to basic amino acid compounds that can be used as potential MMPIs for treatment pathologic conditions or disorders mediated wholly or in part by MMPs.	[134]
Aug.25, 2009	US7579486	 X=O, S; R_1--R_4=H, organic substituent	The provided 6-memdered heterocyclic compounds comprise an organic substituent (e.g. R_3) and two or more ZBGs covalently attached, which can be used as potential MMPIs, histone deacetylase inhibitors (HDACIs), or anthrax lethal factor inhibitors (LFIs) for the treatment of preventing or treating a pathology, condition or symptom that is associated with aforementioned enzymes.	[135]

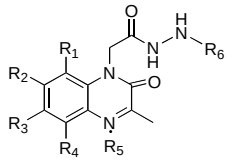
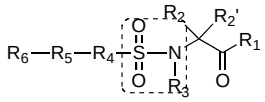
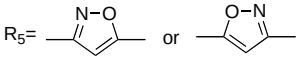
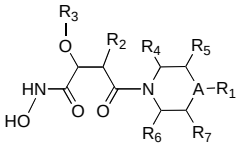
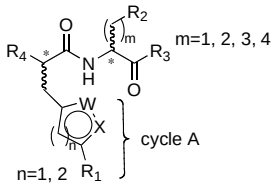
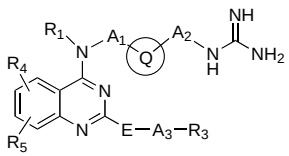
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Sep.17, 2009	WO2009113320	 (I) R_1=(*E*)-3-phenylallyl group or a 3-phenylpropyl; R_2=H, isobutyl, 2-(4-methoxyphenyl) ethyl; R_3=1H-indole-3-yl, 1-napthyl, etc; R_4=CH_3, benzyloxy, hydroxyl, phenethyl.	The invention provides a hydroxamic acid-based derivative with excellent MMP inhibitory effect and reduced side-effects.	[136]
Sep.17, 2009	WO2009113736	 (I) R_1=phenyl group that may have 1~3 lower alkoxy groups as substituents on the phenyl ring, R_2=pyridyl group that may have 1~3 carboxyl groups as substituents on the pyridine ring.	The mentioned thiazole derivatives possessing MMP-2 and/or MMP-9 inhibitory activity.	[137]
Sep.23, 2009	CN101541789	 (I) R_1=H, CH_3, C_2H_5, CF_3, cyclopropyl; R_2=H, CH_3.	The invention relates to novel hydantoin derivatives that are useful as MMPIs, particularly interest as potent and selective inhibitors of MMP-12.	[138]*
Sep.29, 2009	US7595327	 J=a monocyclic or bicyclic 5-8 membered cycloalkyl ring, etc; R_2, R_4, R_5=H, alkyl(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), etc; R_3=naphthyl or bicyclic heteroaryl, etc; R_8, R_9=H, OH, OR_{17}, $OCOR_{12}$, $NR_{12}R_{13}$, halo, alkyl(C_{1-6}), alkenyl(C_{2-6}), cycloalkyl(C_{3-8}), etc; E=-CH=CH-, -C=N-, -N=C-, S, O; X=O, S, SO, SO_2, NR_{12};	The invention relates to a group of β-sulfonamide hydroxamic acid derivatives which might be selective, orally bioavailable non-peptide inhibitors of TACE and/or MMPs. Thus, they will be highly desirable for the treatment of the disease states mediated by the mentioned enzymes, such as RA, COPD, stroke, and type II diabetes.	[139]*
Oct.1, 2009	WO2009118292	 R_1=aryl, heteroaryl, heterocycloalkyl, etc; R_2,R_3=H, alkyl(C_{1-7}), X=H, NH_2, CN, halogen, NO_2, alkyl-S-, alkyl-SO_2-, R_5CO, alkyl-SO-, H_2N-SO_2-, alkyl, R_4O; R_4,R_5= alkyl, aryl, arylalkyl, heterocycloalkyl, etc.	The present invention provides novel arylsulfonamide-based compounds or pharmaceutical acceptable compositions that are useful as inhibitors of MMPs such as MMP-2, -8, -9, -12 and -13.	[140]
Oct.6, 2009	US7598240	 n=3 or 4; R=C_2H_5, H; R_1=halogen, alkoxy, haloalkyl, haloalkoxy	The novel benzothiazin-3-one compounds exhibit an excellent pharmacological activity on an arthrosis deformans animal model when orally administered, which are useful as MMPIs. Furthermore, these compounds, acting as prodrugs, can be converted to highly active carboxylic acid derivatives by hydrolysis of its ethoxycarbonyl group in its metabolism in a living body.	[141]
Dec.24, 2009	US20090318511	 R_1=CN, alkyl, R_4O, R_5CONH, R_6CO; R_4, R_5, R_6=alkyl, aryl, etc; R_2=alkyl, arylalkyl, heteroarylalkyl, monoalkylamino-alkyl, heterocyclylalkyl, di-alkylamino-alkyl; R_3= alkyl, cycloalkyl.	The invention provides novel hydroxamic acid -based compounds that are useful as inhibitors of MMPs such as MMP-9, -12 and -13.	[142]

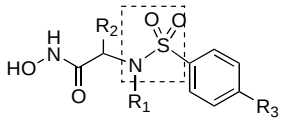
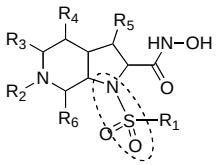
(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Feb.4, 2010	US2010029699	 (I) A, D=alkyl(C_{1-6}), CH=CH-alkyl(C_{1-4}); B=O, S, SO, SO_2, CO, CR_7R_8, $COOR_{14}$, etc; E=substituted aryl, heteroaryl, etc; Q=optionally substituted 5- or 6-membered aryl or heteroaryl; X=O, S, SO, SO_2, CO, CNR_5, $CNOR_5$, etc; Y=CR_5OR_{11}, CS, CO, SO_2, SO, etc; R_1, R_1', R_3=H, alkyl(C_{1-6}), alkylaryl(C_{1-4}); R_2=$COOR_{12}$, CH_2OR_{12}, $SONHR_{12}$, etc; R_4=substituted aryl or heteroaryl, Z=CH_2, O, S, SO, SO_2, NR_5, etc.	The invention provides the said compounds (I) and their physiologically functional derivative as potential MMPIs, in particular, inhibitors for MMP-12.	[143]
Feb.11, 2010	US20100035943	 (IA) (IB) X=O, S, NH; R_1=H, OH, SH, alkyl(C_{1-6}), F, Cl, CF_3, alkoxy(C_{1-6}), alkenyl(C_{2-6}), phenyl, NH_2, phenylalkyl(C_{1-6}), etc; W=HO(C=O), H(C=O)N(OH), HONH(C=O); R_2=R_{10}-$(X)_n$-$(ALK)_m$; R_{10}=H, alkyl(C_{1-5}), CN, NH_2, halo, NO_2, oxo, COOH, $CONH_2$, aryl, etc; ALK=a straight or branched divalent alkylene(C_{1-6}), alkenylene(C_{2-6}), etc; m, n=0, 1; R_3=natural or non-natural α-amino acid; R_4=alkyl(C_{1-6}), alkenyl(C_{2-6}), phenyl, cycloalkyl, naphthyl, etc.	The invention relates to therapeutically active hydroxamic and carboxylic acid derivatives as effective dual MMP-9/12 inhibitors.	[144]
Mar.11, 2010	WO2010028051	 (I) (II) HET=5- or 6-membered heterocycle, i=0, 1; R_1=hydrocarbyl, heterocyclo; R_2=H, hydrocarbyl, substituted hydrocarbyl, etc; R_{3a}, R_{3b}=H, hydrocarbyl, substituted hydrocarbyl (i=1); X_1=cation, H, acyl, etc. X_2=NX_{20}, $NX_{20}O$, $NX_{20}CR_{22}R_{23}$, etc. X_{20}=H, hydrocarbyl, heterocyclo, acyl, sulfonyl, thionyl, phosphonyl, etc; X_{23}, X_{24}=H, hydrocarbyl, etc.	The invention relates to substituted heterocyclic mercaptosulfonamide compounds, precursors, and derivatives, which are designed to be potent and selective inhibitors of MMPs.	[145]
Apr.1, 2010	US20100081610	 (I) * Selected from (*R*,*R*),(*S*,*S*), (*R*,*S*) and (*S*,*R*); n=1-5; R_1=H, optionally substituted alkyl, alkenyl, alkynyl, heterocyclyl, cycloalkyl, aryl, heteroaryl, aralkyl, alkoxy, aryloxy, alkenyloxy, alkynyloxy; R_2=heterocyclyl, NR_4R_5, heteroaryl, $NHC(=Y)R_4$, $NHSO_2R_4$, NHC(=O)OR, $C(=Y)NR_5$, $C(=O)OR_6$; R_3=H, F, alkyl, cycloalkylalkyl, aralkyl; A=OH, OR_4, *O*-acyl, $NHSO_2R_4$, NH_2, NR_5, $OC(=O)NR_5$, etc; Q=substituted aryl or heteroaryl.	The invention claims β-hydroxyl and amino-substituted carboxylic acids that act as dual MMP-9/12 inhibitors, which have desirable activity profiles and beneficial potency, selectivity, pharmacokinetic properties and/or improved physicochemical properties as compared to racemic compounds.	[146]
May.5, 2010	CN101701032	 R_1, R_2, R_3, R_4=H, alkyl(C_{1-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), heteroalkyl, cycloalkyl(C_{3-12}), which can be substituted by other substituents, such as halogen, NO_2, aryl, acyl, aryl, acyl, OH, NH_2, acylalkyl(C_{1-8}), etc; R_5=L-amino acid methyl/ethyl esters, substituted primary or secondary amines. R_6=pharmaceutically acceptable inorganic or organic acids, such as saturated or unsaturated alkyl acids, etc.	The invention provides a group of quinoxalinone scaffold-based peptidomimetic derivatives and their pharmaceutically acceptable salts, which have definite effects of MMP-2 (gelatinase A) inhibitory activities. These compounds might be therefore developed into potential antitumor leads.	[147]

(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
May.12, 2010	CN101704792	 R_1, R_2, R_3, R_4=H, alkyl(C_{1-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), heteroalkyl, cycloalkyl(C_{3-12}), which can be substituted by other substituents, such as halogen, NO_2, aryl, acyl, aryl, acyl, OH, NH_2, acylalkyl(C_{1-8}), etc; R_5=pharmaceutically acceptable inorganic or organic acids, such as saturated or unsaturated alkyl acids, etc. R_6=alkyl(C_{1-8})carbonyl, substituted arylcarbonyl, heteroarylcarbonyl, L-amino acid acyl, aliphatic/aromatic imide, alkyl(C_{1-8})sulfonyl, substituted aromatic sulfonyl, heteroaryl sulfonyl.	The invention provides a group of quinoxalinone scaffold-based hydrazides and the pharmaceutically acceptable salts, which have definite effects of MMP-2 inhibitory activities. These compounds might be therefore developed into potential antitumor leads.	[148]
Nov.2, 2010	US7825146	 R_1=NHOH, OH, lower alkyloxy; R_2,R_2',R_3=H, lower alkyl,aryl, etc; R_4= substituted phenylene or thiophenylene; 	The invention relates to sulfonamide derivatives with an isoxazole ring having the potential inhibition against MMPs, especially excellent enzymatic inhibition against plural MMP-2, -8, -9, -12 and -13 with subnanomolar activities.	[149]*
Jan.11, 2011	US7868009	 C_1--C_7=alkyl(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), cycloalkyl(C_{3-8}), heteroalkyl(C_{1-12}), aryl (e.g. phenyl, naphthyl, phenantrenyl and the like), alkyl(C_{1-6})aryl, arylalkyl(C_{1-6}), heteroaryl, alkyl(C_{1-6})heteroaryl, carboxyalkyl(C_{1-6}), etc.	The invention presents N-hydroxyamide derivatives as useful and selective inhibitors of the gelatinase (MMP-2, -9) and metalloelastase (MMP-12) which can be potential drugs for the treatment of autoimmune, inflammatory, cardiovascular, neurodegenerative, respiratory diseases, and cancer as well.	[150]
Mar.3, 2011	WO2011023864	 n=1, W, X=O, N, C; n=2, W, X=C; R_1=phenyl, biphenyl, 1,2,3-thiadiazole, 3'-chlorophenyl, phenoxymethyl, pyrimidine, 1-methyl-1H-pyrazole, thiazole, thiophen, etc. m=1, R_2=carboxylic acid, 4-hydroxyphenyl, 7H-imidazol, OH, isopropyl, CH_3. m=2, R_2= carboxylic acid, carboxamide. m=3, R_2=carboxylic acid; m=4, R_2=NH_2. R_3=NH_2, carboxymethyl piperidine, carboxymethyl 3-aminophenyl, L- or D-glutamate, etc. R_4=H, carboxymethyl, CH_2COOH.	The invention relates to pseudo-dipeptidiques derivatives or their pharmaceutical composition which are hopeful to be used as selective MMP-12 inhibitors. Among the compounds, cycle A represents cycle and/or heterocycle substituted or unsubstituted benzene, isoxazole, which play an important role in the power of inhibition towards the MMPS.	[151]
Mar.3, 2011	US7915267	 R_1=H, alkyl; ring Q=cyclohexylene, phenylene; A_1, A_2=a single bond or alkylene; E=NHCO, $CONR_2$; R_2=H, alkyl; A_3=A_{31}-A_{32}-A_{33}; A_{31}----A_{33}= a single bond or saturated/unsaturated aliphatic hydrocarbon groups; R_3=substituted acyclic aliphatic hydrocarbon groups (C_{1-8}); R_4, R_5=H, alkyl, alkoxy, halogen.	The invention relates to heterocyclic amide derivatives showing a superior MMP inhibitory activity (especial the MMP-13), which can be potential drugs for the prophylaxis or treatment of MMP-13 related joint diseases, such as OA, RA and the like.	[152]

(Table 1) Contd….

Publication Date	Patent No.	Chemical Structure	Brief Characteristics	Ref.
Apr.13, 2011	EP2308837	 R_1=alkyl group which can be substituted with one or more substituents (e.g. OH, SH, NH_2, NHR', X-glucide, X-glycoaminoacid, X-glycopeptide, etc). R_2=H, alkyl, substituted alkyl comprising from O, S, N, C, etc. R_3=H, OH, alkyl, aryl, oxoalkyl, oxoaryl.	The invention offers arylsulfonamido-substituted hydroxamic acid derivatives that are useful as inhibitors of MMPs, with especial selectivity against MMP-8, -12, -13 and a much lower enzymatic inhibition of MMP-7. The present compounds, possessing good water solubility and anti-aging properties, are particularly useful for the treatment of various pathological events associated with MMP-12-overexpressed states, such as pulmonary emphysema, periodontitis, and so on.	[153]*
Apr.26, 2011	US7932389	 C_1—C_6=alkyl(C_{1-6}), alkenyl(C_{2-6}), alkynyl(C_{2-6}), cycloalkyl(C_{3-8}), heteroalkyl(C_{1-12}), aryl (e.g. phenyl, naphthyl, phenantrenyl and the like), alkyl(C_{1-6})aryl, arylalkyl(C_{1-6}), heteroaryl, alkyl(C_{1-6})heteroaryl, carboxyalkyl(C_{1-6}), etc.	The invention is related to octahydropyrrolo[2,3,c]pyridine derivatives, the pharmaceutical composition, which are useful MMPIs, in particular as inhibitors of the gelatinase (MMP-2, -9) and metalloelastase (MMP-12). Therefore, they can be suitable for the treatment and/or prophylaxis of disorders related to autoimmune, inflammatory, cardiovascular, neurodegenerative, respiratory conditions, and cancer as well.	[154]*

- Means important MMPIs with particular interests, these compounds display either potent or highly selective MMP inhibition, which might develop into potential anticancer drugs.

ver, they are not susceptible to degradation *in vivo* via inactivation of other enzymes [174]. As a consequence, natural or small molecular synthetic MMPIs have become an area of intense interest in both academic and pharmaceutical industry in recent years. Especially, the pivotal role of several MMPs in multistep processes of tumor invasion and metastasis, including proteolytic degradation of ECM, migration and angiogenesis, as well as arthritis makes it an attractive target for cancer or arthritis therapy. More importantly, inhibitors targeting this class of enzymes are likely to be cytostatic rather than cytotoxic so there is expectation that they may be better tolerated than current cytotoxics and more potent than conventional clinical drugs [175].

Since the late 1970's when the beginning of the first drug candidate targeting this enzyme family, more than two decades have been spent to develop new families of natural and synthetic MMPIs, or optimize the chemical structures of existing compounds with clear MMP inhibitory activities so as to find candidates having acceptable pharmacological, pharmacokinetic and selectivity profiles. Accordingly, a wealth of MMPIs have progressed into various developmental stages for different symptoms, mostly in cancer, arthritis and other diseases associated with tissue remodeling (e.g. cardiovascular disease). The vast majority of them are proved to be broad-spectrum inhibitors, exemplified by batimastat and marimastat [176].

However, clinical trials conducted on these broad-spectrum inhibitors have yielded disappointing results, especially in the cancer pathology area. Most of them from both preclinical and clinical have even been hampered mainly due to poor bioavailability, poor selectivity, or poor target validation for the targeted therapy and undesirable side effects, such as tissue toxicity, the promotion of liver metastasis, and the most frequent occurring musculoskeletal syndrome (MSS, also called tendonitis-like fibromyalgia) that manifested itself as musculoskeletal pain, tendonitis and inflammation [177]. As a result, even with tremendous improvements in the development of MMPIs over the past few decades, these questions still remain unsolved today and, simple and effective drugs for inhibiting individual MMPs have not been approved and marketed for the treatment of any diseases in any mammal. So far, antibiotic doxycycline still remains the only FDA medically approved MMPI with μM range inhibition used in the therapy for periodontal disease [178].

Challenges of MMPI Research

As mentioned above, the first challenge, also the toughest issue doubtless, is that there are no specific inhibitors for any particular MMP enzyme subtypes currently. Most identified MMPIs are broad-spectrum inhibitors that inhibit many MMP family members simultaneously because the catalytic

domains of most MMPs possess similar structures (e.g. catalytic zinc ion) and/or functions. Even if effective *in vitro*, the adverse effects (e.g. the most frequent MSS) can easily occur *in vivo* or in preclinical trials [179, 180]. Consequently, achieving selective inhibition of certain MMP subtypes to, at least in part, conquer the MSS has become the primary and most challenging goal [181]. However, identifying the mechanism of the MSS symptoms has not yet reached agreement and how MMPs contribute to MMS is complicated and not well understood.

At present, it is generally acknowledged that several factors may account for the causes: 1) MSS is attributed to the widely used broad-spectrum MMP inhibition. 2) MSS is related to the inhibition of certain MMP(s). For example, MMP-1 and/or MMP-14 (MT1-MMP) inhibition was once considered to be the cause of clinical MSS and this led to the development of MMPIs (e.g. prinomastat) without inhibiting the enzymatic activity of MMP-1 and/or MMP-14, yet this hypothesis turned out to be unworkable in clinical trials [182, 183]. 3) Inhibition of certain MMP(s) also affects other non-MMP proteases whose prime structure is similar with MMPs. For instance, BMS-275291 was designed to avoid inhibition of the ADAM (a disintegrin and metalloproteinase) family of proteases, whose catalytic domain is very similar to MMPs, yet MSS was still unavoidable eventually [184]. 4) Myriad of evidence suggests hat the side effects are likely derived from the off-target metal chelation since the inhibitors also coordinate with other enzymes with the same metal ions presumably [185].

Apart from the dose-limiting MSS, the second challenge comes from our limited knowledge of the precise mechanisms by which this family of enzymes maintains their biological functions *in vivo*. Considering MMP family members have complex correlation with different physiological processes some of which can accelerate disease progression while others might have irrelevant, or even protective and beneficial functions (e.g. MMP-8) [186], it is reasonable to believe great efforts still needed to carefully delineate their physiological roles in normal and pathologic conditions.

The third might partly flow from the inappropriate evaluation towards most of MMPIs in preclinical or clinical trials. This is because rational designing a systematic and comprehensive evaluation for a given drug candidate is rather complex. Take MMPI-evaluation as an example, since MMPIs are cytostatic rather than cytotoxic agents and, they do not kill tumor cells, conventional evaluation of efficacy such as decreased tumor size, therefore, could not be used to monitor activity. Additionally, these enzymes play especial roles in the early steps of tumor evolution and expand their pro-tumorigenic properties. Yet in preclinical/clinical trials, MMPI was, in most cases, administered at later stages, where their effectiveness might be severely weakened [187].

Possible Strategies to Design Potent MMPIs

In light of the clinical complexity associated with MMPIs, there is a compelling need for the identification of more effective and selective MMPIs that possess an improved clinical application. At the same time, multiple failures of MMPI drugs in clinical trials has resulted in the reconsideration that how to conquer the drawbacks of these broad-spectrum MMPIs. Commonly, a desirable MMPI with potential selectivity would avoid side effects associated with inhibition of MMPs that are not involved in the pathogenesis of the diseases being treated. To achieve this, three possible strategies can be identified hereby.

The first is the high-throughput screening (HTS) approach of a large number of randomly selected samples from natural or non-natural compounds. Despite many advantageous features of screening rapidly and efficiently, there are also many unresolved issues. For example, the results from the *in vitro* screening model may not be consistent with the *in vivo* effects; there has not yet a unified standard towards the screening model; and so on [188].

The second and also the most important is the structure-based drug design (SBDD) approach in combination with computational resources, which relies on prior acquaintance of the 3D structure of target enzyme to design entirely new leads with desired biological properties. In fact, no new MMPIs are now developed without the structure-based guidance, and the increasing availability of high-resolution x-ray crystal structures for many members of this protein makes MMPs ideally suitable for structure-based design approaches. Most available MMP structures are presented as the complexes of the catalytic MMP domains with various peptidic, peptidomimetic or non-peptidic inhibitors [189-193]. Besides, the growing combinatorial chemistry and computational resources, as well as the quantitative structure-activity relationship (QSAR) studies by using COMFA, GRID and CoMSIA approaches has accelerated the development of inhibitors with high-affinity, which might be elaborated into potential drugs [194-196]. Furthermore, all these studies, in turn, provide useful information in elucidating the mechanisms of chemical-biological interactions for certain MMP subtypes.

Additionally, Whittaker *et al*. also provided us some useful information that the affinity of potential MMPIs depends primarily on three factors: i) a suitable backbone to recognize the target enzyme through a hydrogen bond interaction or other van der Waals interactions so as to achieve improved binding potency; ii) a zinc-binding group (ZBG) as functional group that capable to efficiently chelate with the catalytic zinc(II) ion; iii) one or more substrate-like hydrophobic fragment(s) stretching to fit the deeper S1' cavity which is the key subsite to determine the primary specificity of MMPs [197].

Of these subsites, the S1' pocket varies the most in both the amino acid composition and size of the pocket, whereas the shallower S2' and S3' pockets are more solvent-exposed with relatively minor enzyme-inhibitor interactions. Generally, the S1' pocket of MMPs is very flexible and can be categorized based on its shape into shallow (MMP-1, -7), medium (MMP-2, -8, -9), and deep (MMP-3, -11, -12, -13, and -14) [198, 199]. These differences are initially thought to exploit selective MMPIs with reasonable potency. For instance, relatively small substituents such as leucine and isoleucine fragments might be considered to introduce into the S1' pocket of MMP-1 and -7 owing to the obstruction of Arg214 and Tyr214 around this domain, respectively. In the case of MMP-3 which can accept a very large substituent in the S1' pocket, long aliphatic or aromatic side chains may be

introduced to penetrate and occupy this area. Fig. (**5**) shows the major binding pockets (S1', S2' and S3') of MMP-8 (PDB ID: 1JAQ).

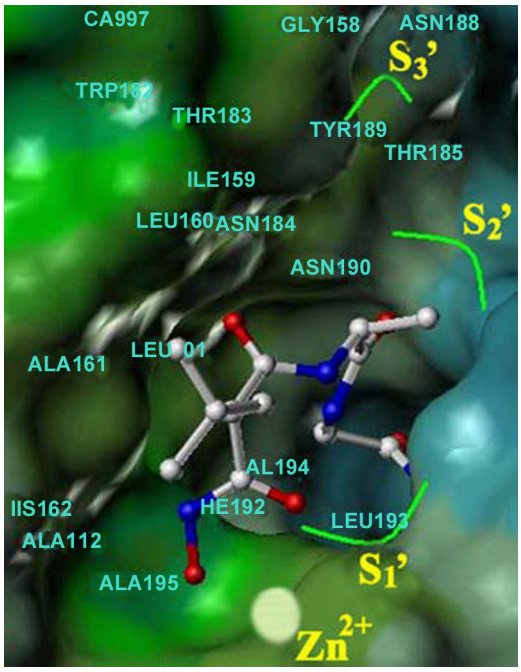


Fig. (5). Schematic Binding Pockets of MMP-8 (PDB: 1JAQ).

The S2' cavity can also be utilized to achieve successful MMPI potency because effective S2' interactions can enhance the physicochemical and pharmacokinetic properties without affecting MMP binding affinity. While elongation along the S3' pocket which is located on the periphery of the MMP active site usually does not yield a strong affinity [200-202]. Of course, it is difficult to predict the exact extension as well as the subsite binding interactions, and computer modeling analysis can be helpful to predict and guide the reasonable orientation.

In the SBDD, a key to gaining potent enzymatic inhibition is the incorporation of a ZBG into peptide or mimic-peptide backbone on either the left-hand side or the right-hand side, or both sides of the cleavage sites. Indeed, exploitation of potential ZBGs is, undoubtedly, still a classical and popular approach to gain potent MMPIs due to the fact that the MMPs cleave their substrates directly with the participation of catalytic zinc ion. Besides this, the ZBG also acts as an anchor to fix the MMPI in the active site and guide the side chains of the inhibitor into the target binding pockets, such as the S1' and/or S2' pockets.

Early typically identified ZBGs include hydroxamate (or hydroxamic acid), reversed hydroxamate, thiols, phosphinate, carboxylates, aminocarboxylate, phosphonic acid, *N*-hydroxy-formamides, followed by derivatives of these ZBGs, such as hydrazide, sulfonylhydrazide, *N*-hydroxyurea, mercaptosulfide, etc. Of these, hydroxamate emerged as the most preferred in early MMPI design stage. This may be accounted for the fact, in addition to the strong chelating ability with zinc ion, the NH group and deprotonated OH group can also interact with the neighboring Ala and Glu residues of the MMPs through a short and strong hydrogen bonding. In the past few decades, a number of hydroxamate-derived MMPIs are available, and many of them have shown outstanding inhibitory activities in preclinical trials. Yet the clinical tests for these compounds have been disappointing because the usage of such strong metal-chelating moiety may bring a range of negative effects (e.g. low oral bioavailability, poor *in vivo* stability, undesirable pharmacokinetic effects) inevitably. For example, as a mono-anionic chelator with overwhelming chelating power, hydroxamate may bind a spectrum of divalent transition metals including zinc ion, leading to lack of specificity. Or the disproportionate binding with the off-target metalloproteases that were not MMPs may prevail over the contribution from the rest portion of inhibitor, precluding other opportunities for enhanced selectivity [203]. Many hydroxamate MMPIs demonstrating MSS are shown to be related to the overwhelming inhibition of other unrelated metalloproteins [204]. In addition, the poor pharmacokinetic properties might attribute to the hydroxamate group, which can be easily metabolized into hydroxylamine, a known carcinogenic agent, through the cleavage of exopeptidases, leading to toxicity in long-term therapy [205]. Additionally, the C-N bond of the hydroxamate can easily change to its *trans*-configuration, resulting in reduced potency and/or accelerate the metabolism of the hydroxamate functionality owing to the sterical hindrance [206].

Based on the aforementioned, when a ZBG is considered for MMPI design, several issues may be concerned. 1) The well-established hydroxamate, carboxylates and thiols, etc. can still be investigated in new MMPI design through careful selection of suitable backbones or optimization of other parts of the compounds for targeting the binding pockets of individual MMPs; 2) To disclose more effective and non-classical ZBGs, such as the newly developed nitrogen-based ZBGs, heterocyclic bidentate, barbiturates, thiadiazole, thiadiazine, imidazolidinedione, and triazolones as well [207]. Now, the new trends include the exploitation of allosteric non-zinc binding inhibitors, devoid of ZBGs. These kinds of compounds show a non-competitive or uncompetitive mechanism of inhibition, thereby, reducing the opportunity of off-target metalloproteinase inhibition [208].

Traditional HTS from random screening of existing library compounds and natural products or SBDD has generated a variety of peptide analogues, also called as pseudo-peptide derivatives, based on the knowledge of amino acid sequence of collagen at the site of cleavage by collagenase. However, peptide analogues have some drawbacks for clinical usage, i.e., proteolytic lability, low bioavailability, rapid excretion, short duration of action, etc. Therefore, many medicinal chemists have focused on the exploitation of compounds with peptidomimetic (also called peptide mimics) or non-peptidomimetic backbones, which can reduce the degradation rate and meanwhile achieve improved selectivity and affinity towards the target enzymes [209, 210].

The third but not the last is the original fragment-based drug design (FBDD) strategy. Typical FBDD approach comprises fragment screening by using biophysical techniques (e.g. nuclear magnetic resonance (NMR), mass spectrometer (MS) and x-ray crystallography, etc.) and the use of obtained virtual hits to construct new lead structures. Fragments are usually part of an elaborated molecule, with low molecular

weight (~100-250Da) and low structural complexity, as well as a high binding efficacy against a therapeutic target of interest. The selected fragments will be served as optimal building blocks for the subsequent combinatorial SBDD and structural optimization, including fragment linking, expanding, growing, and/or fusing etc, to achieve suitable molecules with desired potency, selectivity and drug-like pharmaceutical properties (lower cytotoxicity, required ADME (absorption, distribution, metabolism, excretion) profiles, and improved pharmacokinetics, etc.) [211, 212]. For instance, from the cited patents, in addition to the widely used sulfonamide- or sulfone functional groups that we have mentioned above, the hydantoin motif as a privileged and drug-like fragment is also very popular in designing potential MMPIs with desirable properties, and some of them demonstrate excellent oral bioavailability or favorable pharmacokinetic profiles [109, 112, 119, 127, 133, 138]. Moreover, various heterocyclic core scaffolds, e.g. (hydro)quinoline, (hydro)isoquinoline, pyridine, pyrimidine, quinoxalinone, can also be utilized as promising drug-like fragments. Based on the FBDD discovery approach, the ubiquitous motifs, obtained either from the databases or the known bioactive molecules, can be utilized as useful scaffolds or substituents to generate desirable MMPI hits.

CONCLUSIONS

Taken together, MMPs can be, in most cases as revealed by amount of studies, implicated in many pathologic courses acting as pivotal effectors, such as wound healing, tissue repair and remodeling, morphogenesis, etc. These correlations might be considered as predictive or prognostic markers to help to resolve pathologic conditions via alteration the dysregulation of specific and/or combined MMPs. Yet, on the other side, increasing evidence indicates that a small number of MMP family members provide a beneficial and/or protective effect, either at the primary or the metastatic stages of cancer progression, while other members seem to be irrelevant to different pathological pathways. Moreover, a severe fact is their role during normal physiological processes is still far insufficient comparing to the well-documented involvement in tumorigenic events, In this regard there is still a pressing need to clarify the structure and function of the individual members of the MMP family. Only in this way is it possible to dig out highly selective inhibitors for therapeutic approaches.

However, since most MMP members share the main structural and functional characteristics, there is considerable functional overlap amongst individual MMPs or other proteases, making the design of selective MMPIs a formidable task. At present, rational drug design (RDD) has been involved in the exploitation of potent MMPIs with selectivity, which requires the help of a wide array of knowledge, ranging from transgenic models to recent proteomic screening. Furthermore, the availability of computational resources such as X-ray crystallographic studies, molecular modeling and dynamics, as well as docking-type techniques has accelerated the MMPIs development. Additionally, molecular pharmacology, molecular oncology and chemoinformatics, together with the technologies of chemogenomics have been successfully applied to develop an in-depth understanding of the multiple roles of MMPs in diseases (especially in cancer), the full repertoire of MMP substrates, and hence the *in vivo* functions of MMPs. All these opportunities have stimulated extensive studies in both academic and industrial laboratories toward the potential MMPIs.

From the recent issued patents with respect to small molecular MMPIs, tremendous effort on the exploitation of therapeutics that can selectively target MMPs remains ongoing. In the future, with the support of gradually revealed mechanisms by which individual MMPs carries out its functions, more and more potent and selective MMPIs with remarkable therapeutically potency will appear, making them amenable for clinical use in the prevention and control of MMP-associated disorders or conditions. Alternatively, future pathologic therapy may consider a combination of a MMPI with other drugs with a clear therapeutic efficacy to achieve a synergistic effect in clinical therapy.

ABBREVIATIONS

AT	=	Alimentary tract
ADAM	=	A disintegrin and metalloproteinase
ADAMTS	=	A disintegrin and metalloproteinase with thrombospondin motif
ADME	=	Absorption, distribution, metabolism, excretion
BAL	=	Bronchoalveolar lavage
BBB	=	Blood brain barrier
bFGF	=	Basic fibroblast growth factor
CAC	=	Colon cancer
COPD	=	Chronic obstructive pulmonary disease
COX-2	=	Cyclooxygenase-2
CPA	=	Cartilage protective agent
ECL	=	Enterochromaffin-like
ECM	=	Extracellular matrix
FBDD	=	Fragment-based drug design
FN2	=	Fibronectin-like type II
HDACIs	=	Histone deacetylase inhibitors
HME	=	Human macrophage elastase
H. pylori	=	*Helicobacter pylori*
HTS	=	High throughput screening
IGF-II	=	Insulin-like growth factor-II
IGFBP	=	Insulin-like growth factor binding proteins
IKK-2	=	IκB kinase-2
LFIs	=	Lethal factor inhibitors
MAPK	=	Mitogen-activated protein kinases
MMPs	=	Matrix metalloproteins
MMPIs	=	Matrix metalloprotein inhibitors
MS	=	Multiple sclerosis
MS	=	Mass spectrometer

MSS	=	Musculoskeletal syndrome
NF-κB	=	Nuclear factor κB
NMDAR	=	NMDA receptor
NMR	=	Nuclear magnetic resonance
NPC	=	Nasopharyngeal carcinoma
NSCLC	=	Non-small cell lung cancer
OA	=	Osteoarthritis
OPN	=	Osteopontin
PI3K	=	Phosphatidylinositol 3-kinase
PNS	=	Peripheral nervous system
QSAR	=	Quantitative structure-activity relationship
RA	=	Rheumatoid arthritis
RDD	=	Rational drug design
SBDD	=	Structure-based drug design
SNPs	=	Single-nucleotide polymorphisms
TACE	=	Tumor necrosis factor-α convertase
TB	=	Tumor bone
TIMPs	=	Tissue inhibitors of metalloproteinases
TNF-α	=	Tumor necrosis factor alpha
VEGF	=	Vascular endothelial growth factor
ZBG	=	Zinc-binding group

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CONFLICT OF INTEREST

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