Molecular Diversity of Hydroxamic Acids: Part II. Potential Therapeutic Applications

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Abstract: A hydroxamic acid moiety has been demonstrated as the key structural element in many highly potent and selective inhibitors against a variety of metalloprotease enzymes, such as MMPs, TACE, HDAC, PDF, etc. Over the last several years, there has been a rapid growth of literature and patent applications dealing with the development of the hydroxamic acid-based inhibitors. This review highlights the most recent examples to show their potential therapeutic applications.

INTRODUCTION

Due to the increasing interests in the development of potent inhibitors against various metalloprotease-based therapeutic targets, chemistry dealing with syntheses of hydroxamic acids has recently gained unprecedented popularity in medicinal chemistry laboratories [1]. Since the first small molecule-based metalloprotease inhibitors, angiotensin-converting enzyme (ACE) inhibitors [2], reached the marketplace for the treatment of hypertension in 1980s, members of disease-related metalloproteases as potential therapeutic targets have grown immensely. They are considered one of the major classes of proteases in the area of drug discovery [3].

The metal-chelating nature of the hydroxamic acid moiety is a critical feature for medicinal chemists to devise small molecules into highly active inhibitors such as inhibitors of MMPs and TACE. In fact, most of the lead compounds targeting these enzymes currently at the development stage possess the hydroxamate group [4,5]. During the last several years, there has been a rapid growth of literature and patent applications dealing with the highly potent hydroxamic acid-based inhibitors of metalloproteases. However, this review only highlights the recent and representative examples to depict their potential therapeutic applications.

MMP INHIBITORS

The matrix metalloproteinases (MMP) are a family of zinc containing enzymes that degrade extracellular matrices [6]. They are excreted by a variety of connective tissue and pro-inflammatory cells including fibroblasts, osteoblasts, endothelial cells, macrophages, neutrophils, and lymphocytes. Most are excreted as inactive proenzymes and then activated extracellularly by serine proteases or other MMPs. Over the last decade the MMP family has grown rapidly. So far, 23 members have been identified, which can be subdivided on similarities of their domain structures or on the basis of preferred extracellular matrix (ECM) substrate [7]. The latter grouping strategy leads to classes of the collagenases (MMP-1, MMP-8 and MMP-13), the gelatinases (MMP-2 and MMP-9), the stromelysins (MMP-3, MMP-7 and MMP-10), and the elastase (MMP-12), although more recently discovered MMP members have not yet been classified.

A role for these enzymes has been implicated in both normal and pathological processes. The loss of control of MMP activity and the elevated levels in MMP expression have been associated with a wide array of disease processes, including tumor metastasis [8,9], rheumatoid arthritis [10], osteoarthritis [11,12], periodontal disease [13], multiple sclerosis [14], and congestive heart failure [15]. The development of inhibitors for these enzymes as potential therapeutic agents for the treatment of cancer and rheumatoid arthritis has recently been an area of intense interest within the pharmaceutical industry [4,16].

A large number of such inhibitors have been identified and disclosed in the literature. The majority of them are hydroxamic acids. Structurally, they can be divided into several groups, including succinyl hydroxamic acid-based inhibitors as exemplified by Marimastat [17], N-arylsulfonyl α-aminohydroxamic acid derivatives such as CGS 27023A [18], and hydroxamic acids containing heterocyclic rings, such as piperazine [19], thiazine [20], thiazepine [20], diazepine [21], etc. Biologically, they can be divided into broad-spectrum inhibitors and selective inhibitors. It was proposed that a broad-spectrum inhibitor was likely to be advantageous for the treatment of cancer, but specific inhibition of the collagenases (MMP-1, MMP-8, MMP-13) would be beneficial for the treatment of arthritis. However, the clinical trials on some broad-spectrum MMP inhibitor-based drug candidates such as Marimastat revealed serious musculoskeletal side effects such as pain and a dose-limiting joint-stiffness which must be reversed by a dosing "holiday" [22]. In order to avoid these side effects observed clinically with the broad-spectrum inhibitor Marimastat, although the hypothesis is still speculative, the development of subtype selective MMP inhibitors, especially sparing interstitial collagenase (MMP-1), has recently been a major focus. A set of representative examples of selective hydroxamic acid-based MMP inhibitors is shown in **Table 1**.

A research group at British Biotech reported a series of selective MMP inhibitors through modification of their lead compound, Marimastat [23]. The structure was first truncated by replacement of the *tert*-butyl glycine P2'

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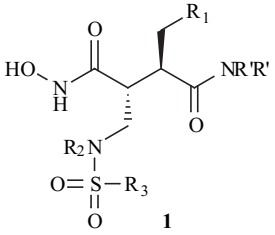
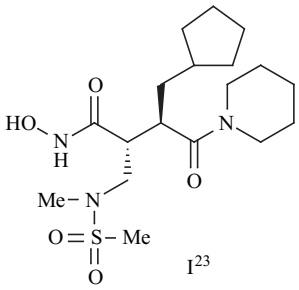
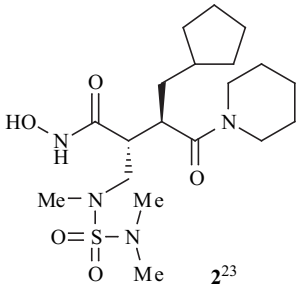
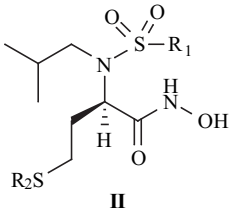
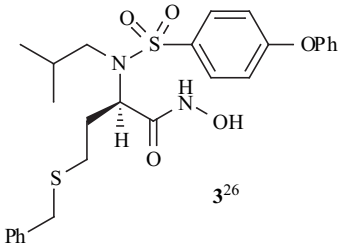
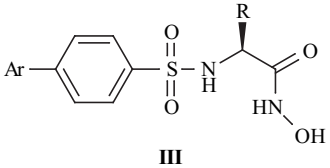
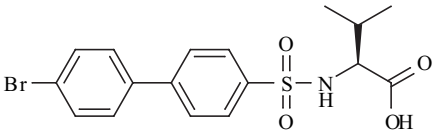
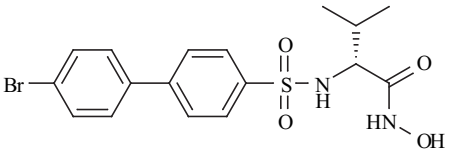
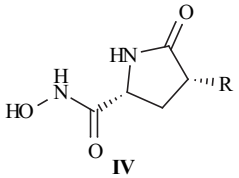
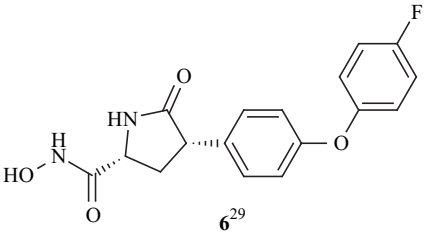
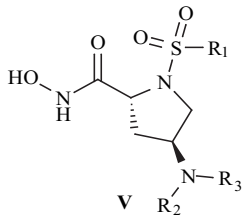
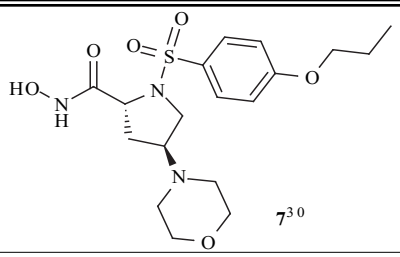
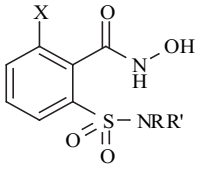
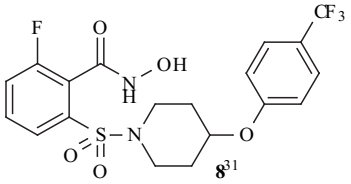
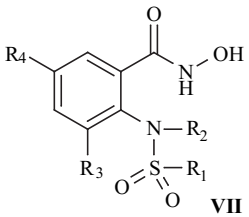
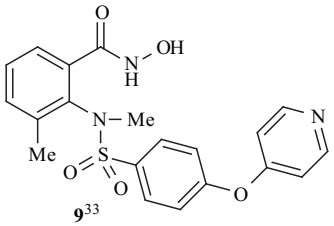
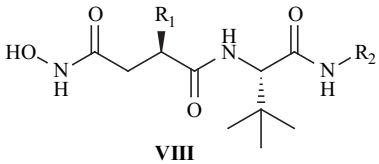
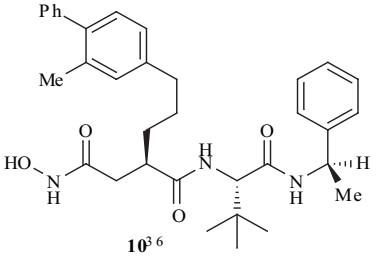
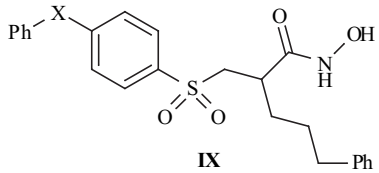
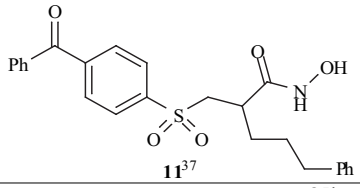
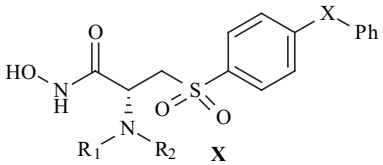
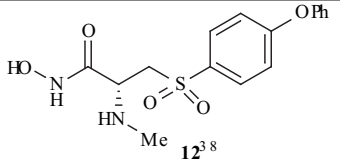
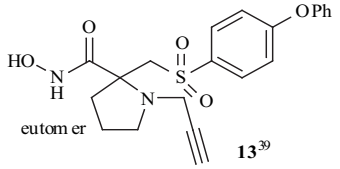
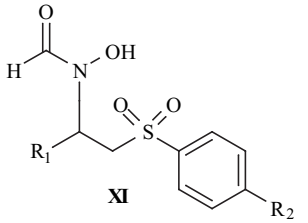
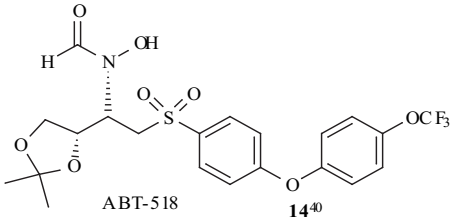
fragment of Marimastat with piperidine. Subsequently, the introduction of a sulfonamido methylene group alpha to the hydroxamic acid provided a different enzyme selectivity dependent on the nature of the sulfonyl substituent. Further increases in potency can be achieved by the introduction of a cyclopentyl methyl group in P1'. As shown in **Table 1**, Compounds (**1**) and (**2**) were found to be 'MMP-1 selective' and 'MMP-1, MMP-8, MMP-13 selective', respectively. Both compounds exhibited good oral bioavailability.

Table 1. Representative Examples of Selective MMP Inhibitors

Templates/Scaffolds	Lead Compounds	Activity(IC_{50})
 **1**	 I[23]	6 nM (MMP-1) 900 nM(MMP-2) 200 nM(MMP-3) 200 nM(MMP-8) 400 nM(MMP-13)
	 **2**[23]	6 nM (MMP-1) 300 nM (MMP-2) 400 nM (MMP-3) 10 nM (MMP-8) 40 nM (MMP-13)
 **II**	 **3**[26]	1450 nM (MMP-1) 1.6 nM (MMP-2) 4.2 nM (MMP-3) 0.5 nM (MMP-9) 3.2 nM (MMP-13)
 **III**	 PD 166793 **4**[27]	6 mM (MMP-1) 4 nM (MMP-2) 7 nM (MMP-3) 7.9 mM (MMP-9) 8 nM (MMP-13)
	 **5**[27]	110 nM (MMP-1) 1 nM (MMP-2) 5 nM (MMP-3) 18 nM (MMP-9) 2 nM (MMP-13)
 **IV**	 **6**[29]	1.56 mM (MMP-1) 39 nM (MMP-2) 703 nM (MMP-3) 82 nM (MMP-9) 7 nM (MMP-13)

(Table 1). contd.....

Templates/Scaffolds	Lead Compounds	Activity(IC_{50})
 **V**	 **7**[30]	490 nM (MMP-1) 7 nM (MMP-3) 16.5 nM (MMP-8) 1 nM (MMP-13)
 **VI**	 **8**[31]	>10 mM (MMP-1) 3.3 nM (MMP-2) 12.2 nM MMP-13
 **VII**	 **9**[33]	3245 nM (MMP-1) 7 nM (MMP-9) 4 nM (MMP-13)
 **VIII**	 **10**[36]	51 nM (MMP-1) 1.8 nM (MMP-2) 5.9 nM (MMP-3) 0.84 mM (MMP-9) 73 nM (MMP-13)
 **IX**	 **11**[37]	2000 nM (MMP-1) 4 nM (MMP-2) 100 nM (MMP-3) 15 nM (MMP-8) 5 nM (MMP-9)
 **X**	 **12**[38]	400 nM (MMP-1) 0.4 nM (MMP-13)
	 **13**[39]	300 nM (MMP-1) <0.1 nM (MMP-2) <0.1 nM (MMP-13)
 **XI**	 ABT-518 **14**[40]	>50,000 nM (MMP-1) 1.5 nM (MMP-2) 5.5 nM (MMP-9)

Hanessian's group undertook a comparative study of fully automated docking programs for reported X-ray and NMR structures of MMP/inhibitor complexes, revealing AutoDock to be reliable and efficient in predicting binding modes observed in the X-ray co-crystals of these inhibitors [24]. Based on the results, the same group designed and synthesized a series of *N*-arylsulfonyl *S*-alkyl homocysteine hydroxamic acids (**II**) with low nanomolar and subnanomolar inhibitory activity toward various MMPs [25,26]. The variations at the P_1, P_1' and P_2' sites revealed a remarkable effect on the potency and selectivity of these compounds against a variety of MMPs. Compound (**3**) shown in **Table 1** exhibited potency against MMP-9 with selectivity versus MMP-1 of 2900 times.

A research group at ex-Parke-Davis (now Pfizer) reported a series of biphenylsulfonamide derivatives, such as a carboxylic analogue (**4**) (PD 166793), as selective inhibitors against MMP-2, MMP-3 and MMP-13 and micromolar potency vs. MMP-1, MMP-7 and MMP-9 [27,28]. Surprisingly, the corresponding hydroxamic acid derivative of (**4**) [(*S*)-configuration at the α-position] significantly decreased activity *in vitro*. Compound (**5**) with (*R*)-configuration regained the potency but showed broad-spectrum inhibitory activity. It was claimed that compound (**4**) displayed the best pharmacokinetics among this series.

Robinson *et al.* at Pfizer discovered a potent pyrrolidinone scaffold-based MMP-13 inhibitor (**6**) by a structure-based design using a homology model of the enzyme derived from MMP-8 [29]. The corresponding carboxylic acid of (**6**) did not show inhibition against either MMP-1 or MMP-13.

Aminoproline scaffold-based hydroxamic acid derivatives (**V**) were designed and synthesized by Natchus *et al.* at Procter and Gamble [30]. Detailed SAR studies for this series were reported. Modification of the P1' portion of the molecules affected both potency and selectivity. Longer-chain aliphatic substituents in this region tended to increase potency against MMP-3 and decrease potency against MMP-1. Compound (**7**) also showed efficacy in a rat osteoarthritis model.

Barta *et al.* at Pharmacia reported a series of novel, MMP-1 sparing arylhydroxamic acid sulfonamides (**VI**) with activity against MMP-2 and MMP-13 [31]. The crystal structure analysis on the complex of compound (**8**) and MMP-8 revealed that the selectivity against MMP-1 was achieved by making P1' moieties of sufficient length to sterically interfere with the Arg residue in MMP-1 that is positionally equivalent to Leu 193 in MMP-8.

A series of papers describing novel anthranilic acid scaffold-based MMP inhibitors (**VII**) has been recently published by Levin *et al.* at Wyeth-Ayerst [32,33,34]. SARs for variation of the 3-, 5-positions and P1' moiety led to the lead compounds with nanomolar level *in vitro* activity against various MMPs and TACE. Compound (**9**) exhibited a high selectivity for MMP-9 and MMP-13 over MMP-1, and displayed both in an oral activity model and in a rat sponge-wrapped cartilage model.

A series of succinyl hydroxamic acids as potent and selective inhibitors of MMP-3 was discovered as reported by Fray *et al.* at Pfizer, UK [35,36]. It was discovered that inhibitory potency against MMP-2 could be dramatically reduced by subtle modifications to P3' group. Compound (**10**), UK-356,618, was the most potent and selective MMP-3 inhibitor reported at that time.

Baxter *et al.* at Celltech disclosed novel arylsulfonyl hydroxamic acids (**IX**) as potent and selective MMP-inhibitors [37]. The lead compound (**11**) exhibited excellent inhibitory potency against MMP-2, MMP-3, MMP-8 and MMP-9, and a superior selectivity profile over MMP-1, and displayed significantly better inhibition in *in vivo* models of arthritis and cancer.

Very recently, a series of α-amino-β-sulphone hydroxamic acids (**X**) was discovered as potent inhibitors of MMP-13 that spare MMP-1 [38,39]. Potency and selectivity may be modulated by varying the P1' moiety. Compound (**12**) also showed good absorption when administered orally to the rat. The same group disclosed that α-alkylated derivatives, such as (**13**), showed highly potent inhibitory activity against MMP-2 and MMP-13.

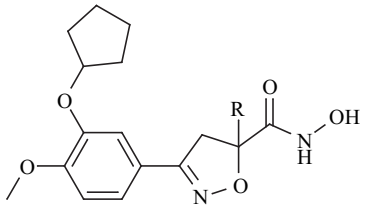
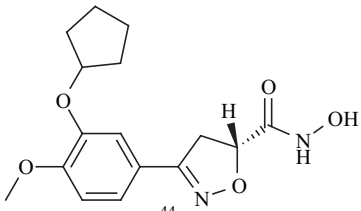
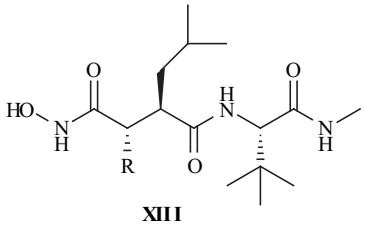
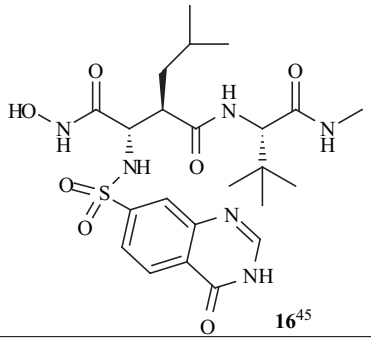
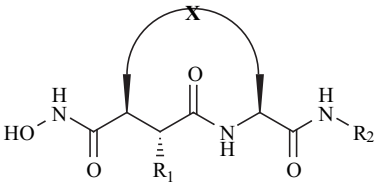
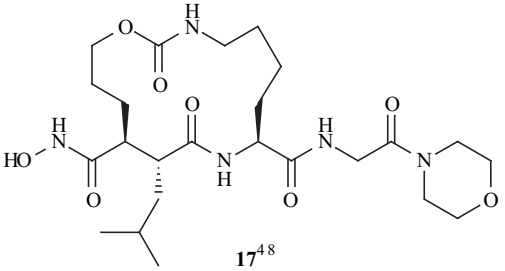
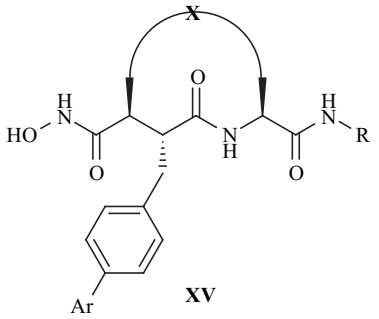
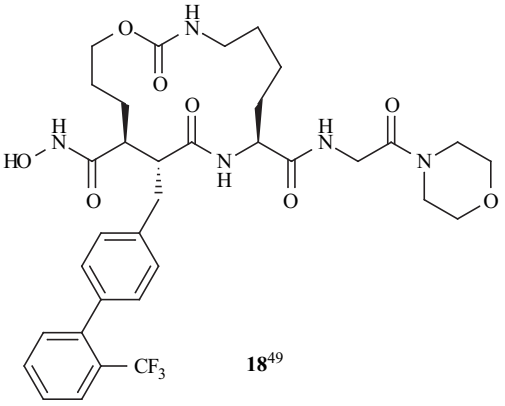
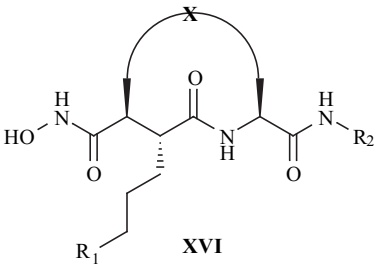
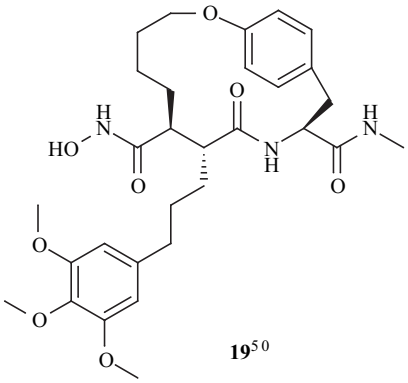
Efforts were also directed toward the development of selective MMP-2 and MMP-9 inhibitors as potential antitumor agents. The Abbott group disclosed a novel series of sulfone *N*-formylhydroxylamine (retrohydroxamic acid) [40]. The lead series is highly selective for inhibition of MMP-2 and MMP-9 over MMP-1. Optimization of the substituent adjacent to the retrohydroxamate center led to the discovery of ABT-518, (**14**), which exhibits significant inhibition of tumor growth in animal models and is currently undergoing Phase I clinical trials in cancer patients.

TACE INHIBITORS

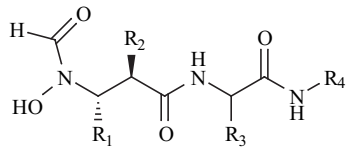
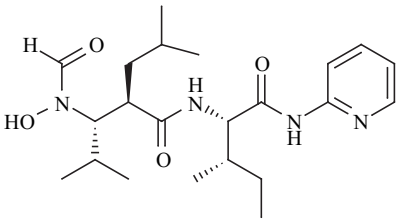
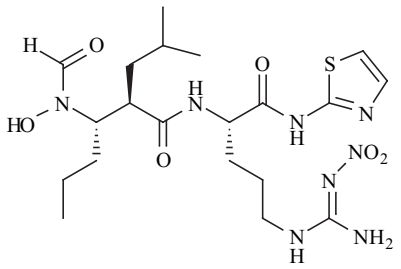
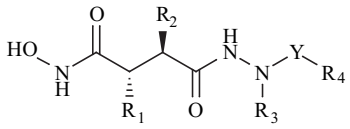
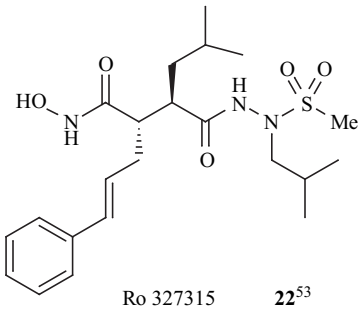
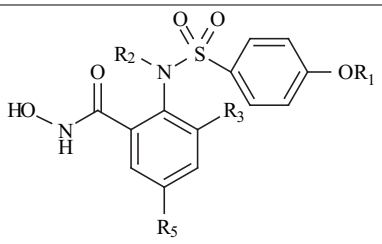
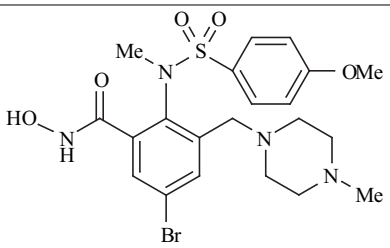
TNF-α as a therapeutic target through inhibition of its production for treatment of rheumatoid arthritis and Crohn's disease has been recently validated by the approval of biologics such as monoclonal antibody (Remicade) [41] and the soluble TNF p75 receptor fusion protein (Enbrel) [42]. Development of small molecule-based anti-TNF-α agents has received great attention in current pharmaceutical industries. One of the approaches is the inhibition of the tumor necrosis factor-α converting enzyme (TACE) which is believed to be responsible for TNF-α processing [5,43]. TACE is a member of the 'A Disintegrin And Metalloproteinase (ADAM)' family. It was found that the active site of TACE is very similar to those of MMPs. In fact, many broad-spectrum inhibitors of MMPs also exhibit the inhibitory potency against TACE. It is very challenging for medicinal chemists to discover highly potent and specific TACE inhibitors which may lead to effective medicines for the treatment of inflammatory diseases with minimum side effects. Some representative hydroxamic acid-based TACE inhibitors are shown in **Table 2**.

In early 1998, Kleinman *et al.* at Pfizer reported a series of hydroxamic acid analogues of a competitive PDE4A inhibitor, rolipram, that showed dual inhibitory activity against both PDE4 and TACE [44].The most potent compound (**15**) showed low nanomolar activity in the inhibition of TNF-α-release in purified human monocytes (HM) and in the endogenous milieu-human whole blood (HWB) assays.

Table 2. Representative Examples of TACE Inhibitors

Templates/Scaffolds	Lead Compounds	Activity[a]
 **XII**	 **15**[44]	30 nM (TACE-WBA) 2.2 nM (PDE4A) 2.1 nM (PDE4B) 18 nM (PDE4C) 2.7 nM (PDE4D)
 **XIII**	 **16**[45]	0.57 nM (TACE) 280 nM (TACE-WBA) 1.3 nM (MMP-1)
 **XIV**	 **17**[48]	Ki values: 4.2 nM (TACE) 67 nM (TACE-WBA) 13 nM (MMP-1) 1.1 nM (MMP-2) 1.2 nM (MMP-9)
 **XV**	 **18**[49]	2.8 nM (TACE) 70 nM (WBA) >2 mM (MMP-1) >2 mM (MMP-2) >2 mM (MMP-9)
 **XVI**	 **19**[50]	7.6 nM (TACE) 140 nM (TNF-THPI) 2300 nM (MMP-1) 110 nM (MMP-2)

(Table 2). contd.....

Templates/Scaffolds	Lead Compounds	Activity[a]
 **XVII**	 GW 3333 **20**[51]	K_i values: 42 nM (TACE) 19 nM (MMP1) 20 nM (MMP-3) 16 nM (MMP-9)
	 GW 4459 **21**[52]	4.3 nM (TACE) 34 nM (TNF-release) 34 nM (MMP-1) 31 nM (MMP-3) 13 nM (MMP-9)
 **XVIII**	 Ro 327315 **22**[53]	K_i = 3 nM (TACE IC_{50} = 375 nM (TNF-THPI)
 **XIX**	 **23**[33]	26 nM (TACE) 194 nM (MMP-1) 2 nM (MMP-9) 5 nM (MMP-13))

a. IC_{50} values unless otherwise indicated.

A different approach leading to the discovery of TACE inhibitors was based on the introduction of α-substitution of the succinyl hydroxamic acid-based derivatives, as reported by Barlaam *et al.* at AstraZeneca [45]. They found that the introduction of bulky α-substituents such as thioethers, sulfonamides and ethers, showed improved potency against TACE compared to Marimastat. Particularly, the sulfonamide series, such as compound (**16**), exhibited high potency in the blood assay as well. However, these compounds were also inhibitors of MMP-1 and MMP-8, and they were not able to demonstrate good efficacy in animal models.

Based on computer modeling and the known crystal structure of MMP-3 and BB-16 (a succinyl hydroxamic acid-based MMP inhibitor), Xue and his co-workers at DuPont Pharmaceuticals designed and synthesized a series of P1-P2'-linked analogues **XIV** [46,47]. They found that macrocycles, such as SC903 and SE205, to be potent inhibitors of MMP-1, MMP-3 and MMP-9. More importantly, these compounds showed activity in inhibiting TNF-α release from LPS-stimulated human whole blood through inhibition of TACE. Another compound (**17**), SP057, was disclosed as a potent TACE inhibitor with Ki value of 4.2 nM in TACE assay. However, it is also a broad-spectrum MMP inhibitor [48]. These molecules served as leads for the discovery of highly selective TACE inhibitors as reported very recently by the same group [49]. The new lead series contains a large biphenylmethyl moiety at P1' position which provides a favorable interaction in a larger S1' pocket in TACE in comparison to MMPs. Remarkably, compound (**18**) exhibited >100-fold selectivity over a panel of 11 MMPs and a cellular activity in the whole blood assay (WBA).

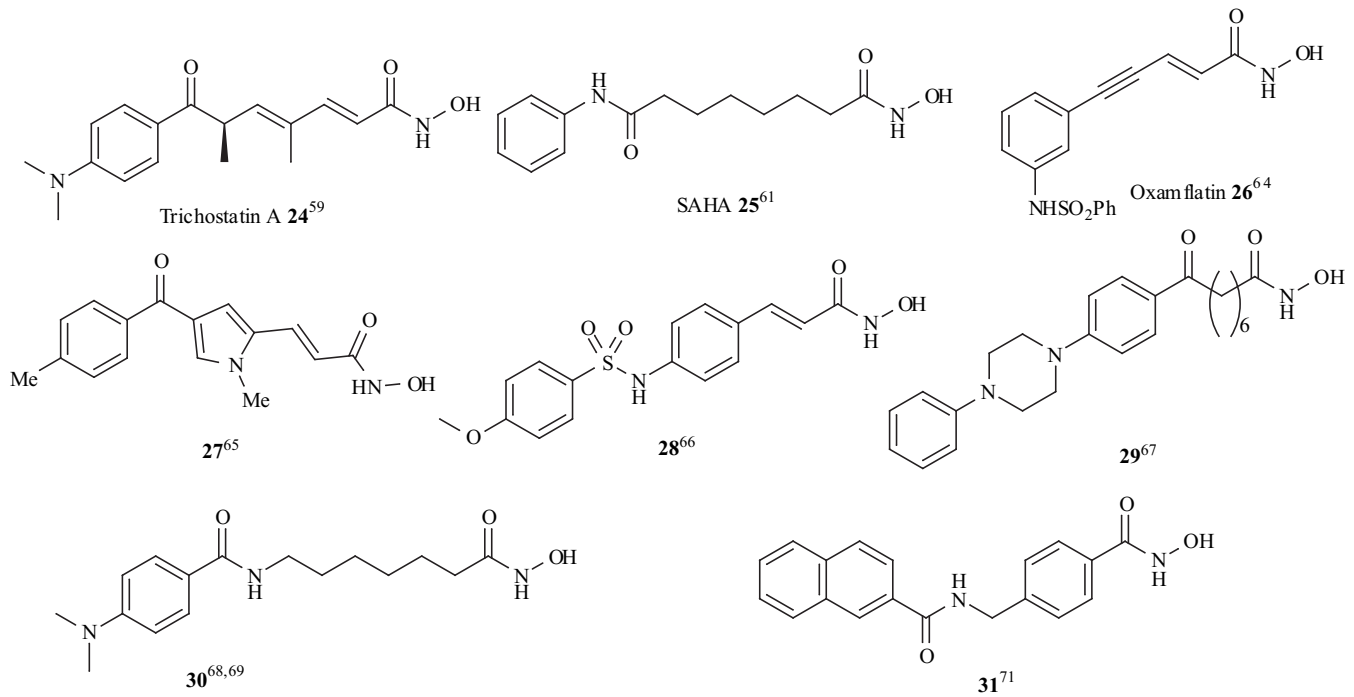


Fig. (1). Representative examples of HDAC inhibitors.

At the same time, Holms *et al.* at Abbott independently discovered a series of selective TACE inhibitors based on modification of the P1' substituent of macrocyclic hydroxamic acid MMP inhibitors previously described by the same group [50]. Compound (**19**) containing a bulky trimethoxyphenylpropyl group showed high selectivity for inhibition of TACE over MMP-1 and MMP-2. It also showed potent activity inhibiting the TNF-α-release in a THP-1 cellular assay.

Retrohydroxamate moiety has been successfully incorporated into the design of TACE inhibitors. GW3333 (**20**) is a highly potent and non-selective (vs. MMPs) TACE inhibitor which has shown greater than 90% inhibition of LPS-stimulated TNF-α production in mice after oral administration (40 mg / kg) [51]. However, it has very low solubility in simulated gastric fluid (SGF). Recently, a new series of inhibitors containing arginine mimetics, which showed increased solubility with better selectivity (TACE vs. MMPs), was described [52]. Compound (**21**) (GW4459) exhibited excellent *in vivo* TNF inhibition when administered via subcutaneous injection.

Succinyl hydroxamic acid-based sulfonylhydrazine analogs were developed as potent TACE inhibitors. Compound (**22**, Ro327315) is currently evaluated in Phase I clinical trials [5,53].

Anthranilic acid derivatives bearing additional amine moieties were evaluated *in vitro* as inhibitors of TACE [34]. The lead compound **(23)** in this series showed promise in developing selective TACE inhibitors.

HISTONE DEACETYLASE (HDAC) INHIBITORS

Recently it was discovered that acetylation of histones is an important step in transcription [54,55]. Acetylation and deacetylation are catalyzed by specific enzyme families, histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. HDACs modulate acetylation of ε-amino groups of lysine located near the N-termini of core histone proteins. Enzyme complexes such as HATs and HDACs have been identified as transcriptional coactivators and transcriptional corepressors, respectively. To date, at least 11 different isoforms of HDAC were described [56]. Although the specific roles of these enzymes and their target genes still remain to be elucidated, deregulation of HDAC activity is implicated in malignant diseases. A link between oncogene-mediated suppression of transcription and recruitment of HDAC into a nuclear complex has been established [57]. Because of their ability to modulate transcription and to induce differentiation and apoptosis in cancer cells, HDAC inhibitors have demonstrated great potential as new anticancer drugs [58]. Some of them have already shown potent antitumor effect *in vivo*, and currently are in clinical trials in cancer patients.

Hydroxamic acid-based HDAC inhibitors represents a majority of known inhibitors reported so far. One of the examples was a natural product trichostatin A (TSA) (**24**) as shown in **Figure 1**. As reported, it exhibited potent and specific inhibitory activity to mammalian histone acetylase both *in vivo* and *in vitro* [59]. The crystal structures of a histone deacetylase-like protein (HDLP) with trichostatin A (TSA) showed that the inhibitors mimic the substrate and that chelation of the zinc in the catalytic pocket by the hydroxamic acid group is the main mechanism of inhibition.[60]

A major breakthrough in finding potent HDAC inhibitors was the discovery of suberoylanilide hydroxamic acid (SAHA, **25**) [61], which is able to induce differentiation and / or apoptosis in a variety of cell types and is currently in phase I clinical trials. So far, the results indicated that SAHA was well tolerated at doses that caused accumulation of acetylated histones in peripheral blood mononuclear cells

and in tumor biopsies. All the patients showed useful response [62,63].

Oxamflatin (**26**) is another hydroxamic acid-based inhibitor which has also shown inhibitory activity against intracellular HDAC. *In vitro*, it showed antiproliferative activity against various mouse and human tumor cell lines with drastic changes in the cell morphology, and *in vivo* it showed antitumor activity against B16 melanoma [64]. A series of pyrrole hydroxamic acid-based HDAC inhibitors was reported recently. However, all the compounds exhibited inhibitory activity only in the micromolar range with the most active derivative (**27**) with IC_{50} of 1.9 μM against maize histone deacetylase HD-2 as the enzyme source [65].

Lavoie and his co-workers at MethylGene disclosed a novel class of sulfonamide hydroxamic acid-based HDAC inhibitors [66]. The successful optimization utilizing the structure-based design led to a highly potent lead series with good *in vitro* and *in vivo* activity. It was claimed that compound (**28**) had significant antiproliferation activity and could induce core histone acetylation at doses as low as 1 μM. The compound also demonstrated *in vivo* efficacy in nude mice bearing subcutaneous non-small cell lung carcinoma A549 tumors. Recently, the same group designed and synthesized a series of structurally simple TSA-like straight chain hydroxamic acid derivatives [67]. Several of the new compounds, such as (**29**), were as potent as TSA in inhibiting HDAC-1 and induced hyperacetylation of histones in T24 human cancer cells and significantly inhibited proliferation in various human cancer cells.

TSA- and SAHA-like straight chain hydroxamic acids were also investigated as potent human HDAC inhibitors by Remiszewski and co-workers [68]. It was shown that enzyme and cellular potency were related to chain length, with n=6 optimal. The most potent compound (**30**) (IC_{50} 46 nM in a human HDAC enzyme inhibition assay) originally developed by Jung and co-workers [69], was found to affect the growth of a panel of eight human tumor cell lines differentially. Recently, Jung and co-workers reported a series of phenylalanine-based straight chain hydroxamic acids with sub-micromolar inhibitory activity against maize HD-2 and with inhibition of proliferation in Friend leukemic cells [70].

Benzohydroxamic acid derivatives were reported as HDAC inhibitors by Uesato and co-workers [71]. The most potent compound (**31**) showed significant anti-proliferative activity with IC_{50} 0.7 μM against HCT 116 human colorectal carcinoma cell lines and potent inhibitory activity in an enzyme assay (human HDAC, IC_{50} 44 nM).

OTHER METALLOPROTEINASE INHIBITORS

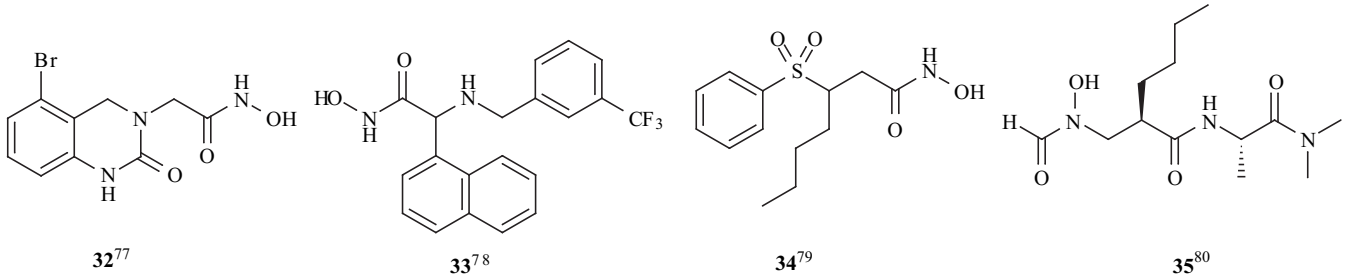
Peptidyl Deformylase (PDF) Inhibitors

Peptidyl deformylase (PDF) is a metalloproteinase, which is believed to be an essential enzyme in both Gram-positive and Gram-negative bacteria [72,73,74]. It catalyzes the removal of a formyl group from the N-termini of polypeptides biosynthesized in prokaryotes. This step in bacterial protein synthesis is essential for bacterial proliferation. Although the validity of PDF as a novel antibacterial target needs to be further confirmed, the search for selective inhibitors of PDF has received attention recently [75,76]. Similar to inhibitors of other metalloproteinases, PDF inhibitors often contain hydroxamic acid moiety as a metal chelating functional group.

Apfel *et al.* reported that low-molecular-weight β-sulfonyl and β-sulfinyl hydroxamic acid derivatives are potent inhibitors of bacterial PDF [77]. Compound (**32**) as shown in **Figure 2** exhibited useful antibacterial activities that cover several pathogens found in respiratory tract infections. However, the development of resistance toward these antibiotics *in vitro* was observed. Thorarensen *et al.* at Pharmacia reported a very potent inhibitor (**33**) against *Staphylococcus aureus* PDF with an IC_{50} in the low nanomolar range [78]. However, the compound did not show antibacterial activity. Potent and selective new inhibitors of the Fe (II) enzyme *Escherichia coli* PDF were reported recently [79]. Again, these compounds, such as (**34**) in **Figure 2**, showed only weak antibacterial activity. The most significant advance in searching for PDF inhibitors in potential antibacterial agents is the discovery of a retrohydroxamic acid derivative (**35**), BB-3497, which was claimed to be orally bioavailable in animal studies [80].

Inhibitors of UDP-3-O-[R-3-Hydroxymyristoyl]-GlcNAc Deacetylase

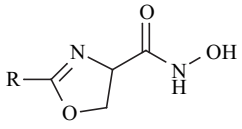
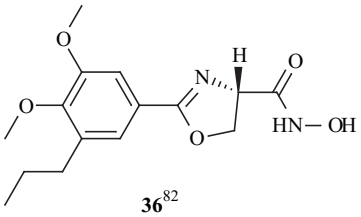
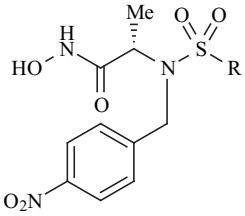
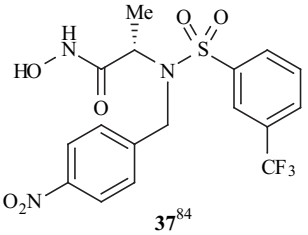
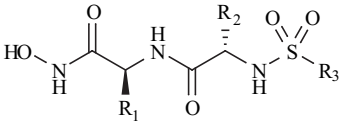
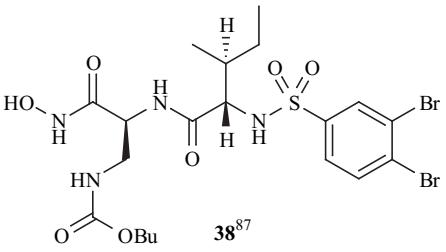
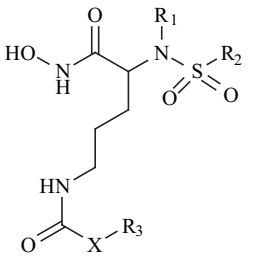
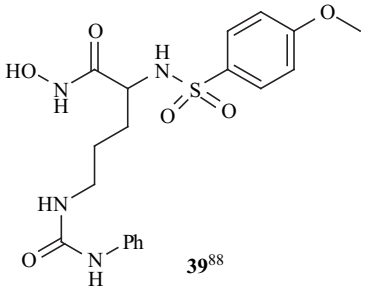
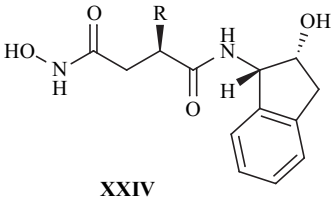
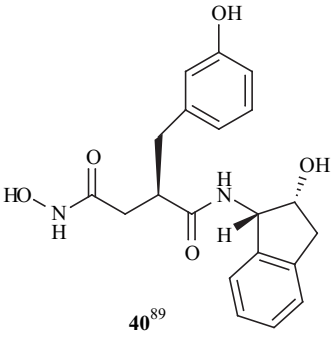
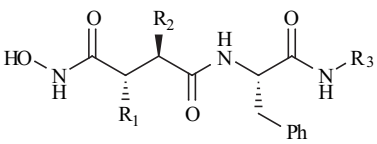
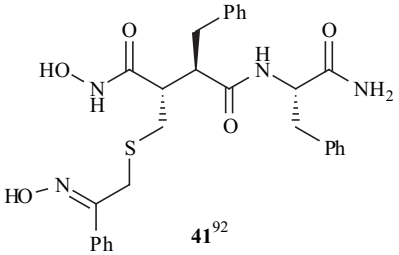
Inhibition of UDP-3-O-[R-3-hydroxymyristoyl]-GlcNAc deacetylase, which is responsible for the second step in lipid A biosynthesis, has been shown as a promising approach for development of novel antibiotics [81]. Chen *et al.* at Merck reported a series of oxazolidine-hydroxamic acid-based inhibitors of this enzyme [82]. The most potent analog L-161, 240, compound (**36**) in **Table 3**, showed an IC_{50} = 30 nM in direct deacetylase assay (DEACET) and displayed an MIC of 1-3 μg/mL against wild-type *E. coli*. However, no antibacterial activity was observed with *Pseudomonas* and *Serratia* even at 100 μg/mL, presumably due to its low permeability.



32[77] **33**[78] **34**[79] **35**[80]

Fig. (2). Representative examples of peptidyl deformylase inhibitors.

Table 3. Representative Examples of Other Metalloprotease Inhibitors

Enzyme	Templates/Scaffolds	Lead Compounds	Activity[a]
UDP-3-O-[R-3-hydroxymyristoryl]-GlcNAc deacetylase	 **XX**	 **36**[82]	IC50 = 30 nM
Clostridium histolyticum collagenase	 **XXI**	 **37**[84]	Ki = 6 nM
Procollagen C-proteinase	 **XXII**	 **38**[87]	IC50 = 26 nM
Procollagen C-proteinase	 **XXIII**	 **39**[88]	IC50 = 50 nM MIC 1-3 mg / mL
Aggrecanase	 **XXIV**	 **40**[89]	IC50 = 130 nM
CD26- processing	 **XXV**	 **41**[92]	IC50 = 130 nM

Clostridium Histolytium Collagenase(ChC) Inhibitors

This enzyme is a zinc-containing protein belonging to the M9 metalloproteinase family, responsible for hydrolysis of triple helical regions of collagen and involved in the pathogenicity of the bacteria which causes human gas gangrene and food poisoning. A series of papers recently published by Supuran *et al.* [83,84,85,86] described the design and synthesis of potent *Clostridium histolytium* Collagenase inhibitors based on sulfonylated L-alanine or glycine hydroxamic acid moiety, such as compound (**37**) in **Table 3**. Many of the compounds showed nanomolar activity for the bacterial collagenase, although *in vivo* activities remain to be seen.

Inhibitors of Procollagen C-Proteinase (PCP)

Overproduction of collagen can lead to many fibrotic diseases, including arthritis and adult respiratory distress syndrome. Prevention of the excessive formation of collagen by inhibition of procollagen C-proteinase would lead to novel medicine for treatment of these inflammatory conditions. Denkwardt *et al.* at Roche Bioscience reported that di- and tripeptide hydroxamic acids, such as (**38**) in **Table 3**, were potent inhibitors of PCP [87]. These inhibitors were designed based on the natural cleavage site of procollagen, and a hydroxamic acid moiety was incorporated as the zinc ligand at the cleavage site with the peptide backbone towards the N-terminal end and succinyl moiety toward the C-terminal end. The same group recently disclosed ornithine-based sulfonamide hydroxamic acids, such as (**39**) in **Table 3**, as potent and non-peptide PCP inhibitors [88]. It was claimed that 200 compounds were synthesized by using combinatorial technology, and the original screening lead was optimized leading to 1000-fold increased potency against PCP.

Aggrecanase Inhibitors

It is believed that aggrecanase plays a pivotal role in the catabolism of aggrecanase in human arthritic diseases [89]. Selective aggrecanase inhibitors may be useful to prevent the progression of joint destruction. By applying an enzyme homology model and the similar biological activity profile of aggrecanase and MMP-8, potent, selective and orally bioavailable aggrecanase inhibitors, such as (**40**) in **Table 3**, were discovered by Yao *et al.* at DuPont Pharmaceuticals [90]. Incorporation of the side chain of a tyrosine residue into the broad spectrum MMP inhibitors as the P1 group raised the selectivity for aggrecanase over MMPs.

CD23-Processing Inhibitors

Using Marimastat as a template, Bailey *et al.* at SmithKline Beecham prepared a series of hydroxamic acids for screening against the enzyme responsible for processing the low affinity IgE receptor (CD23) [91,92]. This enzyme is believed to be a metalloproteinase and plays a pivotal role in the control of IgE [92,93,94]. Selective inhibitors, such as (**41**), were discovered through an appropriate substitution at the α-position and introducing a P1' benzyl group.

CONCLUSIONS

The hydroxamic acid moiety is the key structural element for potency of the inhibitors against these metalloprotease enzymes. However, the selectivity of the inhibitors towards various metalloproteases depends on the structures of the templates or scaffolds as well as the variations of the substituents. The recent efforts in developing MMP inhibitors have demonstrated that higher selectivity can be achieved by manipulating P_1'to P_3' substitutions as well as incorporating potential important interaction between the inhibitors and the proteases at the nonprime side (P_1 substitution). The importance of the structural diversity has also been proven in the discovery of highly selective TACE inhibitors. A combination of the traditional substrate- and mechanism-based approaches and the new technologies such as the structure-based drug design as well as combinatorial chemistry will be essential for the future development of specific protease inhibitors. Success stories in human clinical trials of new hydroxamic acid-based chemical entities are certainly expected.

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