Structure–Activity Relationship Studies of Hydroxamic Acids as Matrix Metalloproteinase Inhibitors

Vaishali M. Patil and Satya P. Gupta

Abstract The chapter specifically deals with the structure–activity relationship studies on various classes of hydroxamates acting as matrix metalloproteinase (MMP) inhibitors. Among all classes of MMP inhibitors, hydroxamates are important in that their zinc-binding group CONHOH makes them a bidentate ligand to act with any metal-containing enzyme. Most of the MMP inhibitors developed by pharmaceutical companies belong to this category of compounds. The position of hydroxamate nitrogen suggests that it is protonated and forms a hydrogen bond with carbonyl oxygen of the enzyme backbone. In addition to zinc-binding affinity, several other properties of the hydroxamic acids depending upon their structures control their MMP inhibition activity. Various categories of hydroxamates such as succinyl, malonic acid, sulfonamide-based, aryl acid-based, sulfone-based, N-benzoyl aminobutyric acids, aminoproline-based, aminopyrrolidine-based, and phosphonamide/phosphinamide-based hydroxamates have been found to act as MMP inhibitors. A detailed structure–activity relationship (SAR) study of all these categories of hydroxamates has been presented.

Keywords Hydroxamates · MMPIs · Succinyl hydroxamates · Malonic acid hydroxamates · Sulfonamide-based hydroxamates · Aryl acid-based hydroxamates · Sulfone-based hydroxamates · Phosphonamide/phosphinamide-based hydroxamates · Structure–activity relationships

Abbreviations

MMP	Matrix metalloproteinase
MMPI	Matrix metalloproteinase inhibitor
QSAR	Quantitative structure–activity relationship

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SAR	Structure-activity relationship
TACE	TNF-α converting enzyme
TIMP	Tissue inhibitors of metalloproteinases
TNF	Tumor necrosis factor-α
ZBG	Zinc-binding group

Contents

1 Introduction

More than 100 years ago, Lossen discovered the first hydroxamic acid and in the present time it is one of the well-studied compounds having numerous applications. The pharmacological potential of hydroxamic acids in a variety of disease conditions, such as viral diseases (Torres 1995; Szekeres et al. 1997), malaria, Alzheimer's disease (Parvathy et al. 1998; El Yazal and Pang 2000), allergic diseases (Igeta et al. 2000; Valapour et al. 2002), tuberculosis (Miller 1989; Shingledecker et al. 2000), cancer, cardiovascular diseases (Jeng and Lombaert 1997), and metal poisoning (Domingo 1998; Weisburger and Weisburger 1973) is well reported. This diverse profile of hydroxamic acids can be attributed to their efficiency in blocking a variety of enzymes, viz., ureases (Zhang et al. 1999; Mishra et al. 2002), peroxidases (Tsukamoto et al. 1999), matrix metalloproteinases (MMPs) (Leung et al. 2000; Hidalgo and Eckhardt 2001), hydrolases (Brown et al. 2004a, b), lipoxygenases (Muri et al. 2002), cyclooxygenases (Dooley et al.

2003; Connolly et al. 1999), histone deacetylases (Marks et al. 2000; Johnstone 2002; Jung 2001; Kelly et al. 2002), peptide deformylases (Chen et al. 2004), etc. In the past decades, an extraordinary work has been carried out on their design, synthesis, and structure–activity relationships (SARs) which support their diverse therapeutic properties (Lipczynska-Kochany 1988). Here we focus on the SAR studies of several groups of hydroxamic acids/hydroxamates relevant to their biomedical applications as matrix metalloproteinase inhibitors (MMPIs).

2 Structural Features of MMPIs

MMPs belong to the family of proteolytic enzymes and regulate a plethora of physiological and pathological functions. Their complex role also contributes to unintended side effects during clinical trials. For more than three decades, MMPs have been heralded as promising targets for the treatment of different diseases as discussed before and scientists have been involved in finding potent inhibitors for them. The unique site specificity and selectivity of MMPIs for different MMP targets (Gupta and Patil 2012) have been the focus of recent research. Over activation of MMPs results in an imbalance between the activity of MMPs and tissue inhibitors of metalloproteinases (TIMPs) that can lead to a variety of pathological disorders (Aranapakam et al. 2003a, b; Venkatesan et al. 2004; Brown et al. 2004a). Although the role of each MMP is not known for certain, the study of their inhibition has evoked great interest. A variety of connective tissues and proinflammatory cells including fibroblasts, osteoblasts, endothelial cells, macrophages, neutrophils, and lymphocytes excrete these MMPs, of which most are expressed as inactive zymogens, that are subsequently processed by other proteolytic enzymes, e.g., serine proteases, furin, plasmin, and others, to generate the active forms. Under normal physiological conditions, the proteolytic activity of the MMPs is controlled at any of the following three known stages: transcription, activation of the zymogens, or inhibition by TIMPs. In pathological conditions, this equilibrium is shifted toward increased MMP activity leading to tissue degradation (Cheng et al. 2000; Kontogiorgis et al. 2005).

Since all MMPs belong to the family of zinc-containing enzymes, all contain, in common, a zinc atom (divalent cation Zn^{2+}), and through this metal atom they affect the amide bond hydrolysis. In the amide hydrolysis, this Zn^{2+} ion is generally tetrahedrally coordinated to three donor groups from the enzyme and a water molecule (Leung et al. 2000; Gupta 2007). Based on the conclusions drawn by various research groups, the basic structural features required for an effective MMPI are: (i) the presence of a functional group, such as a carboxylic group (COOH), hydroxamic group (CONHOH), and sulfhydryl group (SH), that may be able to chelate the active site Zn^{2+} ion of the enzyme (such a group is referred to as a zinc-binding group, ZBG), (ii) at least one functional group capable of hydrogen bonding with the enzyme backbone, and (iii) one or more side chains that can have effective van der Waals interactions with the enzyme subsites. Based on these

requirements, a large number of synthetic MMP inhibitors (MMPIs) have been reported by various research groups from industry and academia (Supuran and Scozzafava 2002).

Many of the MMPIs have been investigated by employing computational methods like substrate-based design (Johnson et al. 1987), structure-based design (Babine and Bender 1997), and combinatorial chemistry (Shuttleworth 1998; Whittakar 1998). In the development of synthetic MMPIs, substrate-based design has been the principal approach and three classes of compounds have been developed, viz, (a) compounds that have amino acid residues on both sides of ZBG, e.g., Pn– —P2–P1–ZBG–P1′–P2′—— –Pn′; (b) compounds that have amino acids residues on only right-hand side of the ZBG, e.g., ZBG–P1′–P2′ ———— –Pn′ and are called right-hand (RHS) inhibitors; and (c) compounds that have amino acids residues on only left-hand side of the ZBG, e.g., Pn– —P2–P1–ZBG and are called left-hand side (LHS) inhibitors (Here P's and P′'s refer to the standard nomenclature of amino acid residues as defined in peptide substrates) (Babine and Bender 1997).

3 Hydroxamates as MMPIs

Among all the classes of MMPIs, the hydroxamates, that contain hydroxamic acid group (CONHOH), have been more extensively studied. The synthetic MMPIs have been categorized in structure-based drug design into three classes, *i.e.,* compounds with amino acid residues on both sides of ZBG, compounds with amino acid residues on only the right-hand side of ZBG, and compounds with amino acid residues on only the left-hand sides of ZBG. Among all these three classes, the right-hand side inhibitors were mostly found to be more potent (Gupta 2007; Whittaker et al. 1999). Further, the hydroxamic acid-based MMPIs have been categorized based on their structural features as:

(1) Succinyl hydroxamates
(2) Malonic acid-based hydroxamates
(3) Sulfonamide-based hydroxamates
(4) Aryl acid-based hydroxamates
(5) Anthranilic acid-based hydroxamates

Hydroxamates are among one of the most explored zinc-binding compounds for the development of MMPIs, and most interestingly the first three MMPIs used to treat cardiovascular diseases are from the hydroxamate category (Whittaker et al. 1999). In 1978, Nishino and Power (1978) first introduced a hydroxamate as a ZBG for designing an inhibitor, thermolysin, which provided an encouragement to develop hydroxamate-containing MMPIs (Moore and Spilburg 1986a, b).

At Pfizer, Robinson et al. (2000) designed some nonpeptidic and sulfonamide hydroxamates with an objective to improve the selectivity and were successful in the development of pyrrolidinone-based hydroxamates, e.g., **a** (Fig. 1), having good

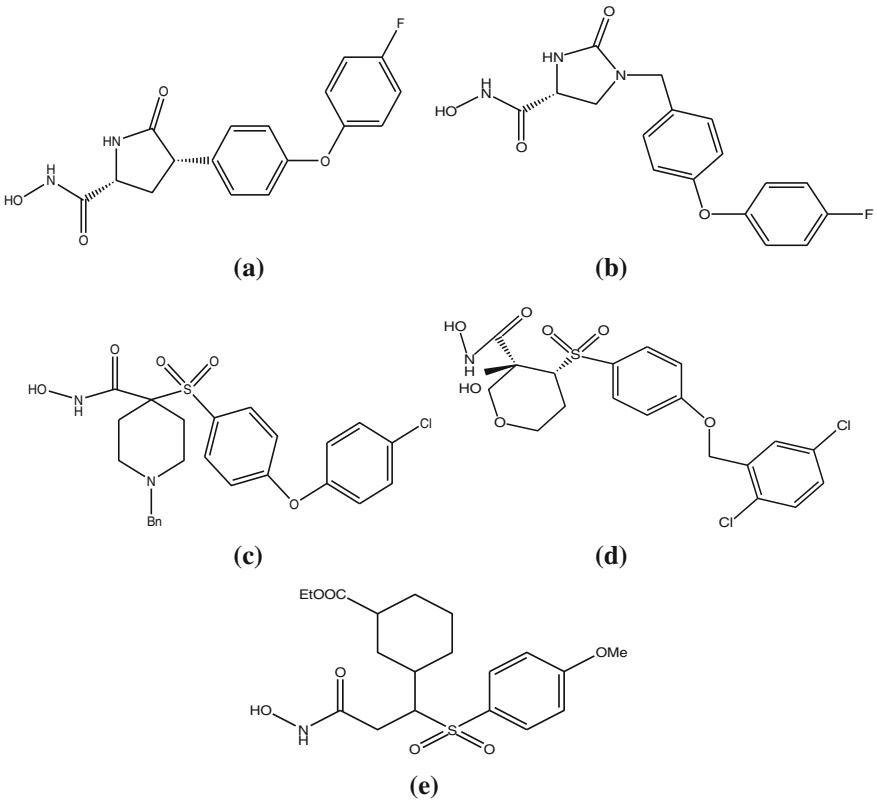


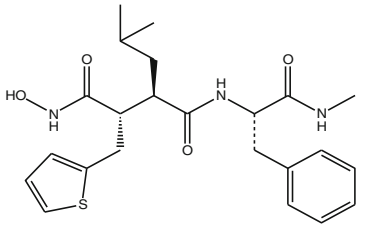
Fig. 1 Structures of some important hydroxamates developed at Pfizer

selectivity for MMP-1. Further structural modifications led to novel series of imidazolidine-based MMPIs, such as **b** (Fig. 1), as strong inhibitors of MMP-13 (Robinson et al. 2001). Simultaneously, compound **c** (Fig. 1) has been developed for the treatment of osteoarthritis (Aranapakam et al. 2003a, b) and SAR studies concluded a better potency of aromatic sulfonyl compounds than that of aliphatic/heteroaromatic sulfonyl derivatives. Some tetrahydopyran-centered sulfone hydroxamates, such as **d** (Fig. 1),were developed as selective inhibitors of MMP-13 at Pfizer (Noe et al. 2004) and further structure optimization led to the development of **e** (Fig. 1) having sub-nanomolar potency against MMP-2 (Salvino et al. 2000).

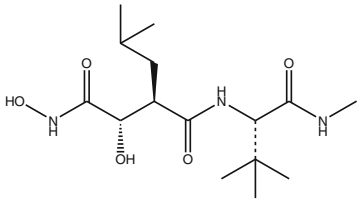
4 Story of Some Clinical Success

The designing of earlier MMPIs was based on the knowledge of the amino acid sequence of collagen at the site of cleavage by MMP-1 (collagenase-1). Among the very first hydroxamates studied, batimastat (BB-94, **1**) and marimastat

(BB-2516, **2**) that were initially found to be clinically useful were the peptidic inhibitors. It was observed that for this type of inhibitors, the presence of a P1′ residue (α to the hydroxamate moiety) leads to a broad-spectrum activity against a variety of MMPs (Whittaker et al. 1999; Bottomley et al. 1998). However, both were withdrawn after clinical trials for cancer due to poor selectivity and poor bioavailability. These studies concluded that compounds which mimicked the sequences of the right-hand side of the cleavage site (primed sites P1′, P2′, P3′, etc.), with a hydroxamic acid moiety incorporated as the zinc-binding group, exhibited better inhibition (Yao et al. 2001).

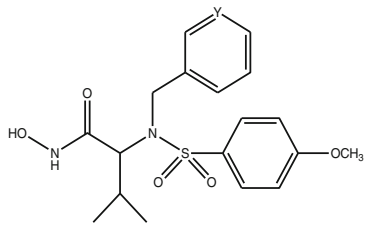


1, BB-94 (Batimastat)

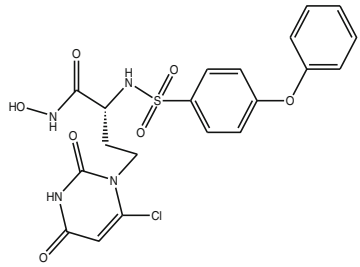


2, BB-2516 (Marimastat)

Among the non-peptide MMPIs, the sulfonamide hydroxamate derivatives CGS27023A (**3a**) and CGS25966 (**3b**) have entered clinical trials (Heath and Grochow 2000). In this case, NMR spectroscopy and the three-dimensional solution structure were used to define the mode of binding with MMP-3 (Zhang et al. 2000). The isopropyl and pyridylmethyl substituents were found to accommodate the hydrophobic S1 and S2′ subsites. Compound **4** from the similar chemical category was found an MMP-13 inhibitor at subnanomolar range (Kimura et al. 2001).



3a; Y=N, **3b**; Y=CH



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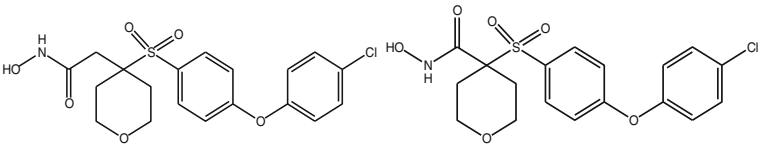
Some sulfone MMPIs (**5**, **6**) having hydroxamic acid moiety were found to have bidentate interactions with MMP-13 in the reported X-ray crystal structures. The selectivity of these compounds for MMP-13 was attributed to their affinity for the S1′ pocket. This class of inhibitors mimics a carbonyl interaction in peptide-based inhibitors and one of the oxygen of sulfone group serves as the hydrogen bond acceptor from the amide group of Leu185. However, of these two, **6** was withdrawn from Phase II clinical trials for osteoarthritis due to musculoskeletal side effects (Tu et al. 2008).



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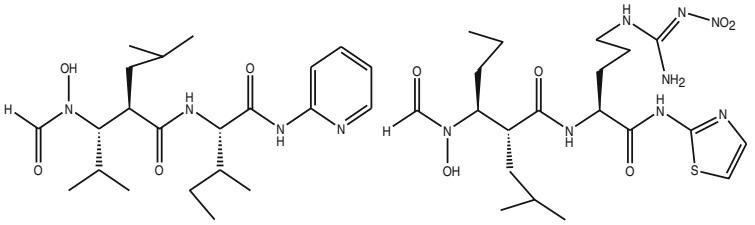
Simultaneously, a series of reverse hydroxamate peptides (**7**–**9**) were reported as broad-spectrum inhibitors of tumor necrosis factor-α (TNF-α) converting enzyme (TACE) and MMPs (Andrews et al. 2000). Compound **7** had IC_{50} values of 19, 20, 16, and 42 nM for MMP-1, -3, -9, and TACE inhibition, respectively, but failed to show any specificity for TACE against MMPs and this may be the reason behind their side effects such as tendonitis and musculoskeletal effects. Compound **9**, prepared in a combinatorial fashion, was found to inhibit MMP-3 and -13 ($IC_{50} > 100$ nM) as well as TACE and TNF-α ($IC_{50} < 100$ nM).



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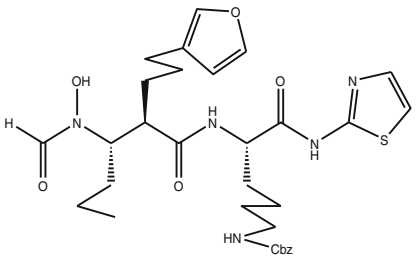

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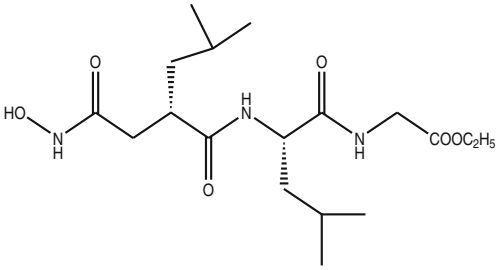
5 SAR Studies

5.1 Succinyl Hydroxamic Acid Derivatives

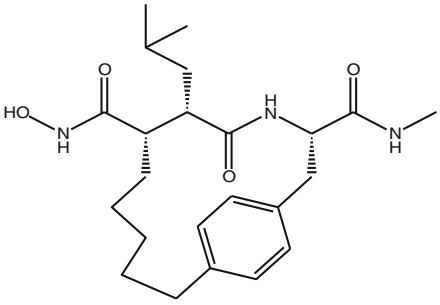
Succinyl hydroxamates have been found to be much stronger MMPIs than those belonging to other groups (Johnson et al. 1987) and thus they have been the most widely studied MMPIs until recently. Compounds **1** (batimastat) and **2** (marimastat) are a few of the potent MMPIs that belong to this category (Whittaker et al.

1999; Supuran and Scozzafava 2002; Levin et al. 2004). Both the compounds showed very good activities in several disease models and another compound (**10**) was found to be orally bioavailable. The bioavailability of **10** was attributed to the presence of a hydrophilic OH moiety at α-carbon, which could probably increase the water solubility of the compound (Levin et al. 2004). Some compounds were obtained by incorporating *cis*-(1*S*, 2*R*)-amino-2-indanol scaffold and optimized as potent, selective, and orally bioavailable inhibitor of



10

aggrecanase. A series of 13- and 14-membered macrocyclic amines, such as **11** and **12**, were developed by linking P1 and P2′ groups of succinic acid-based inhibitors. The selectivity profile of compound **12** against MMP-8 and -9 was attributed to the macrocyclic template and the long phenylpropyl P1 group accommodating in the deep S1 pocket.



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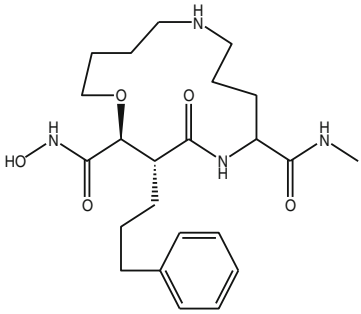

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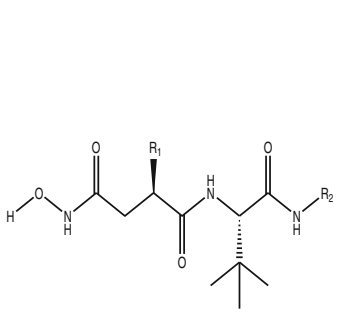
A large series of succinyl hydroxamates (**13**) having variations in P1′ and P3′ groups and P2′ as *t*-butyl group had been evaluated against MMP-2 and -3 (Fray et al. 2001; Fray and Dickinson 2001). The SAR conclusions drawn in the studies were that at P1′ position, the phenylpropyl substituent was conducive to MMP-2 and -3 inhibition and that the *o*-F and *o*-Me at phenyl ring showed remarkable improvement in MMP-3 selectivity as compared to larger groups like Et, OMe, and CF_3 which caused significant loss of activities. These authors concluded that the size of R_1- and R_2-substituents contributes toward MMP-2 selectivity. At R_2 position, the Me and *t*-Bu groups were well tolerated in comparison to the cycloalkyl group. It was also noted that chirality of R_2 plays an important role, i.e., *R*-enantiomer retains potency similar to Me analog against MMP-3 but leads to a loss of potency against MMP-2. Compound **14** was identified as a potent and

selective MMP-3 inhibitor having 303 times selectivity against MMP-2 (Fray and Dickinson 2001).



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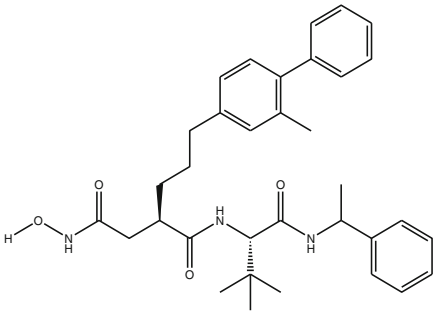

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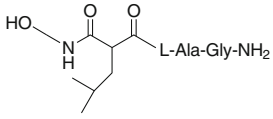
5.2 Malonic Acid-Based Hydroxamates



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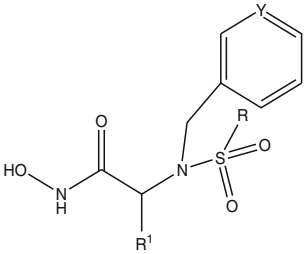
The malonic acid-based hydroxamates were observed to exhibit nonsubstrate-like binding, e.g., compound **15** binds with the Zn^{2+} of MMPs in the same manner as normal hydroxamates do, but its secondary binding is quite different. The C-terminal Ala-Gly-NH_2 moiety adopts a bent conformation that is inserted into the S1′ pocket. Thus, it exhibited nonsubstrate-like binding to the active site and consequently represented a new interesting lead for obtaining malonic acid-based MMP inhibitors (Roedern et al. 1998; Krumme et al. 1998). The SAR studies have shown hydrophobic interactions at S1 subsite of the substituents like isobutyl, $(CH_2)_2Ph$, CH_2Ph, or Ph. For S1′ subsite the OEt and *N*-morpholide were not favored while the C-terminal aromatic groups were found to improve inhibitory potency. There is further improvement in activity with NH-*n*-octyl substituent.

5.3 Sulfonamide-Based Hydroxamates

Sulfonamide-based hydroxamates, as represented by **16**, contain a sulfonamide moiety and involve hydrogen bonding as well as direct hydrophobic interaction with S1′ pocket to improve the enzyme-inhibitor binding. Some of these inhibitors (**3**, **4**) were reported to act as efficient MMPIs (Shuttleworth 1998; Whittaker et al. 1999; Supuran and Scozzafava 2002) and further change in their structural features

could lead to better inhibitors (Jeng et al. 1998; Whittaker et al. 1999; Hannessian et al. 1999).



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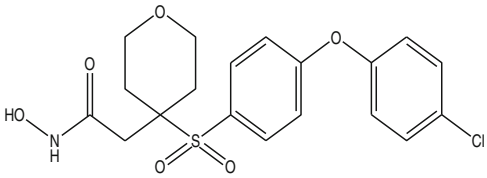
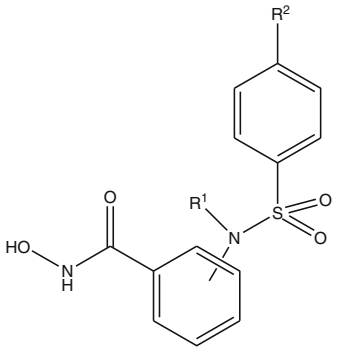


17

Y= H, Cl, NO_2; R = alkyl, aryl
R^1 = H (Gly derivatives), Me (Ala derivatives),
i-Pr (Val derivatives), *i*-Bu (Leu derivatives)

While analogs of **16** were found to possess nanomolar potencies against MMP-1, -2, -8, and -9 (Supuran and Scozzafava 2002), **17** (a sulfone derivative) was observed to be very strong, highly selective, and orally bioavailable MMP inhibitor (Whittaker et al. 1999).

All the sulfonamide-based hydroxamates studied were derived from α-amino acids, with a single sp^3-hydridized carbon atom separating the sulfonamide nitrogen and the zinc chelating hydroxamic acid moiety. Assuming that an increase in this separation, with connecting atoms held rigidly, may lead to more potent compounds, Levin et al. (2001) attempted to design aryl acid-based sulfonamide hydroxamates as represented by an anthranilic acid-based scaffold (**18**). They prepared three regioisomeric (*ortho*, *meta*, and *para*) analogs of **18** with $R^1 = CH_2Ph$ and $R^2 = OCH_3$. Of these, the *ortho* analog **19** was found to be the most potent inhibitor with an IC_{50} value below 1 μM against MMP-1, -9, and -13.



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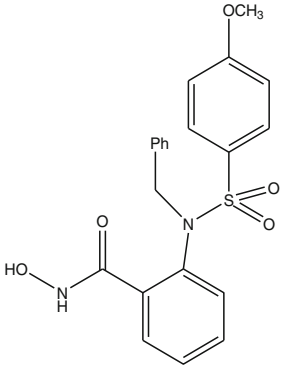

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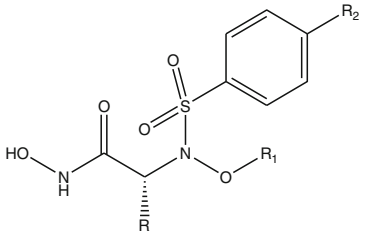
Similarly, a new class of *N*-substituted arylsulfonamido-based hydroxamic acid inhibitors was developed by Rossello et al. (2004) having at the sulfonamido

nitrogen either an oxyalkyl side chain (**20**) or simply an alkyl side chain (**21**), instead of simply hydrogen atom.



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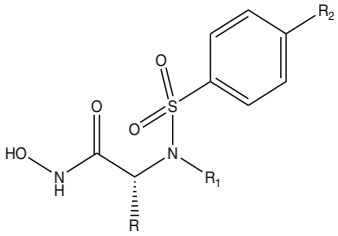

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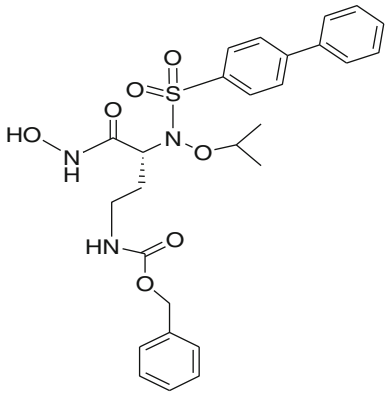
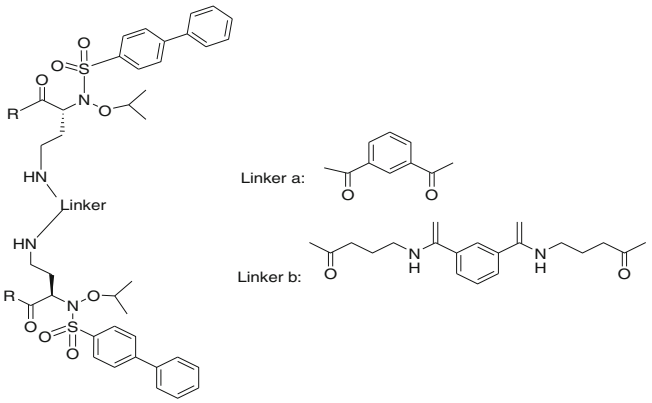
Compounds belonging to the series of **20** were found capable of blocking tumor cell invasion by potent and selective inhibition of MMP-2 and -9. Compound (***R***)-**22**, an analog of **20** with *R*-configuration at carbon α to hydroxamic group, showed a very good inhibitory activity profile toward MMP-2, -9, and -14 with IC_{50} equal to 0.41, 16, and 7.7 nM, respectively (Rossello et al. 2005a).



(*R*)-22

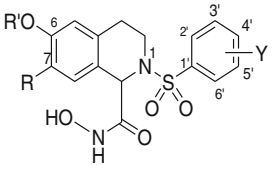
In continuation to this, Rossello et al. (2005b) further reported some twin hydroxamic acids ((***R,R***)-**23**) using some suitable linkers as 'a' and 'b'. Among the series, only compounds having hydroxyl and hydroxylamine substituents at R-position had shown activities against MMP-1, -2, -9, and -14, but were found to be poorly active as compared to the monomeric compound (***R***)**-22**. The hydroxamic acid moiety was found to be essential as proven by the loss of activity of carboxylic analog toward MMP-2 and -9 and it was not evaluated against MMP-1 and -14.



(*R*,*R*)-23

In a series of tetrahydroisoquinoline-based sulfonamide hydroxamates (**24**) studied by Ma et al. (2004), most compounds were found to display potent inhibition activity for some selected MMPs and it was observed that

- The variation of substituents at the 6- and 7-positions and arylsulfonyl group showed marked differences in potency and selectivity and also imparted some subtle isozyme selectivity. Thus these positions plays some role toward activity as seen by alteration of activity due to 6-hydroxyl/benzoxyl and 7-methoxy substituents.
- Among the 6-hydroxy analogs, the 4′-Me substituted derivative was found to be more potent than 4′-H or 4′-OMe substituted, however, the latter was found to be the most favored for MMP-15 inhibition.

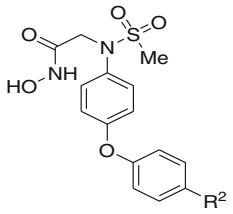


24

Yang et al. (2008) reported a few promising series of *β*-*N*-biaryl ether sulfonamide hydroxamates (**25**–**30**) as novel gelatinase (MMP-2 and -9) inhibitors, in which analogs of **28** were observed to have great selectivity for MMP-9/MMP-2 over MMP-1. Here the group attached to the sulfonamide nitrogen is referred as P1′. Some preliminary SAR conclusions were derived which demonstrated the advantage and potential of a *β*-*N*-biaryl ether sulfonamide moiety in the design of MMP inhibitors.

- The pairing of methanesulfonyl group with biaryl ether type P1′ moiety affords single-digit nanomolar activity against MMP-9.

- A *β*-*N*-biaryl ether sulfonamide with a methyl substituent at P1′ (**28**; R = H; IC_{50} = 6.6 nM) was found to be about 5-fold more potent than an *α*-*N*-biaryl ether sulfonamide (**25**; R^2 = Me; IC_{50} = 31 nM) against MMP-9.
- The introduction of small *α*-substituents (such as OMe/OH/Me at R-position) in **28**, **29,** and **30** and the chirality of the *α*-position (*R vs. S*) in **26** and **28** had marginal influence on the IC_{50} and potency.
- Various substituents on the sulfonamide had the rank order for potency against MMP-2 and -9 as: methyl > ethyl > *n*-propyl > *iso*-propyl > NMe_2 > phenyl.
- The potency was restored to double-digit nanomolar range against MMP-9 on replacing the phenyl with a benzyl group at R^1-position.
- The preference shown by analogs having *para*-substituted phenyl moiety at R^1-position in **29** for MMP-2 over MMP-9 enzyme could be attributed to the tunnel-like S1′ subsite of MMP-2, which shows better tolerance of the longer P1′ moiety than the S1′ pocket of MMP-9.
- In **29,** R_2 = Cl or CH_3 was observed to be more important than any other R_2-substituent.
- Replacement of the phenyl ring with a heteroaryl moiety in **29** (Y = N) was found to reduce potency as the hydrophobic residues surrounding the S1′ pocket typically favor a more lipophilic P1′ moiety.



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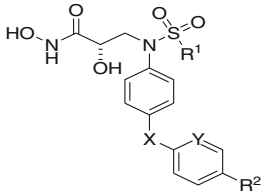

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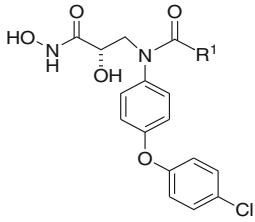

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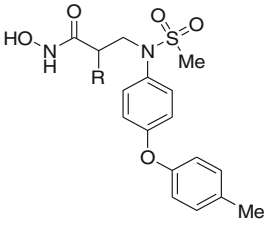

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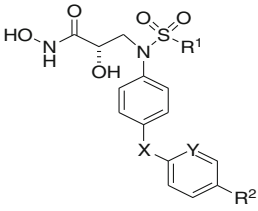

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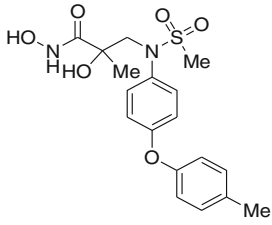
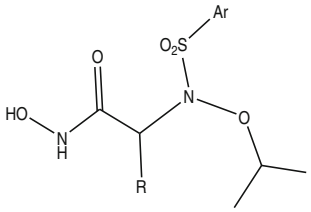


30

In a new series of arylsulfonamidic scaffold (**31**), selective for MMP-13 inhibition (Nuti et al. 2009), the following structure–activity relationships were observed.



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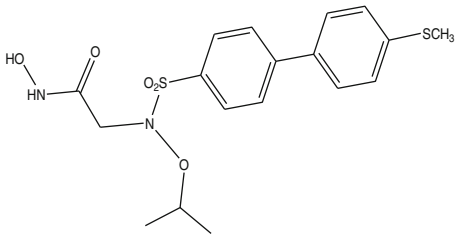
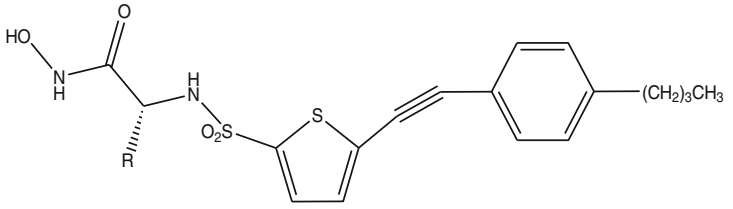


32

The 4-substituted biphenyl group at Ar was found contributing toward the inhibitory profile especially against MMP-2 as compared to the unsubstituted biphenyl for all tested enzymes without affecting the selectivity profile. Among the various substitutions on biphenyl moiety, the 4-methylthio (**32**) and 4-chlorobenzoxy substituents were found to be most significant for inhibition of MMP-13 (IC_{50} = 7.2 and 19 nM, respectively). It also exhibited a slight to good selectivity over MMP-1, -2, -3, -14, -16, and TACE. Compound with an isopropyl group as P1 substituent (R-substituent) was identified to be a promising slow-binding inhibitor of MMP-13 at nanomolar concentration, but with very high selectivity for it as compared to MMP-1, -14, and TACE.

In a series of 4-butylphenyl(ethynylthiophene)sulfonamido-based hydroxamates (**33**) studied by Nuti et al. (2011) for the inhibition of MMP-3, -8, -9, -14, and -25 and for the effective treatment of glioma, a compound having benzophenone substituent (R = –PhCOPh) was identified to have nanomolar potency against MMP-2, -9, and -25 but to be weaker against other members of MMP family. It was also observed that the MMP-2 inhibition activity of **33** was governed by its P1′ group, i.e., 4-butylphenylethynylthiophene, but its enzyme's selectivity profile by its P1 group (α-substituent). The elongated α-chain contributes toward selectivity. The compound with benzophenone moiety was indentified to have highest selectivity over MMP-1, -3, -8, and -14.

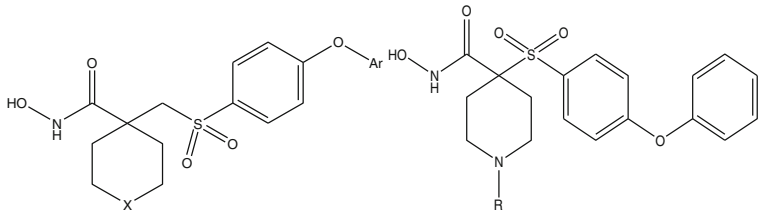


33

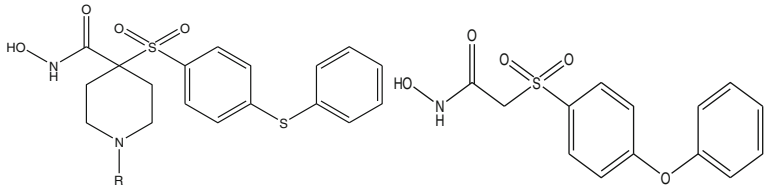
5.4 Sulfone-Based Hydroxamates

Some α- and *β*-piperidinesulfone hydroxamic acids (**34**–**38**) were studied by Becker et al. (2005) as potent inhibitors of MMP-2, -9, and -13. Among them, **35**

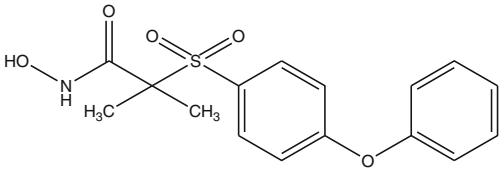
with R = propargyl (SC-276) was selected for further development as it demonstrated excellent antitumor activity against MX-1 breast tumor in mice when dosed orally as monotherapy or in combination with paclitaxel. This work culminated in the discovery of a thioether sulfone hydroxamate (**36,** R = propargyl) having excellent efficacy in murine xenograft tumor models and antiangiogenesis assays and exhibited excellent potency for target enzymes and selectivity against MMP-1. The unsubstituted α-sulfone (**37**) maintained good inhibitory potency against MMP-13 (IC_{50} = 5 nM) and -2 (IC_{50} = 2.6 nM) and was selective against MMP-1 (IC_{50} = 6600 nM). It was, therefore, concluded that the α-sulfone hydroxamates could be developed as potent MMP inhibitors (Becker et al. 2001b; Barta et al. 2003). Consequently, Beckers et al. (2001a) prepared an α,α-dimethyl analog (**38**) that had nanomolar potency better that *β*-sulfones against MMP-13 and -2 (IC_{50} = 0.25 for MMP-13 and 0.1 for MMP-2).



34 **35**



36 **37**

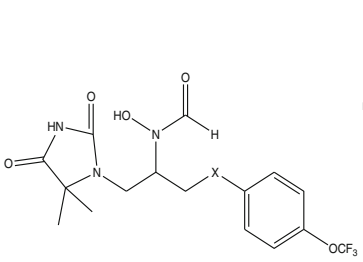


38

5.5 Sulfone N-Formylhydroxylamines (Retrohydroxamates)

An *N*-formylhydroxylamine (retrohydroxamate) **39** (ABT-770) was investigated by Curtin et al. (2001) to be a potent inhibitor with selectivity for inhibition of MMP-2 over MMP-1. It was moderately active against MMM-9. But in the next

communication, the same group of authors (Wada et al. 2002) reported that the replacement of the ether group of **39** by sulfone group led to a compound (**40**) which had substantially increased MMP-9 inhibition activity but with a loss of selectivity for inhibition of MMP-2 and -9 over MMP-1 and diminished oral exposure. Further, replacement of the biphenyl P1′ substituent in sulfone retrohydroxamates with a phenoxyphenyl group provided compounds (**41**) that were highly selective for inhibition of MMP-2 and -9 over MMP-1. In this series, optimization of the substituent R adjacent to the retrohydroxamate center in this series led to a clinical candidate (**42**, ABT-518) which was found to be a highly potent, selective, and orally bioavailable MMP inhibitor that could significantly inhibit tumor growth in animal cancer models.



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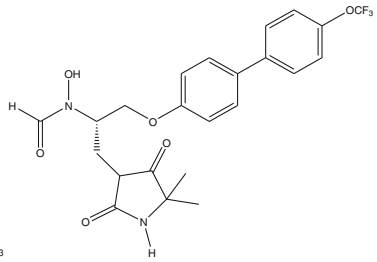
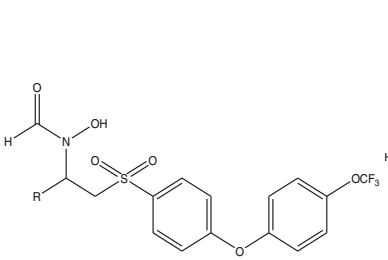


40 (ABT-770)



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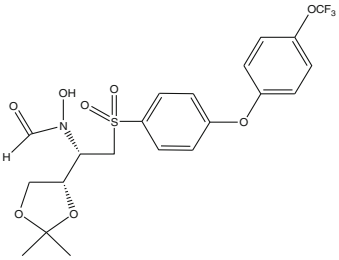
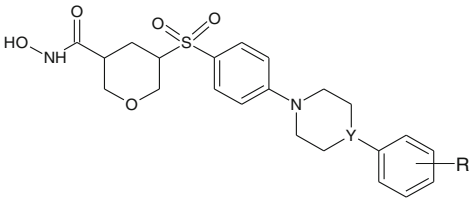
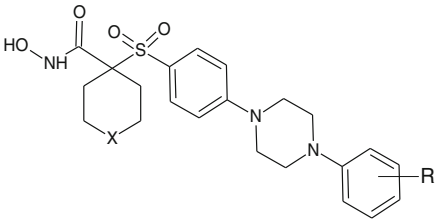


42 (ABT-518)

A small library of *N*-aryl piperazine α-sulfone hydroxamic acid derivatives was designed to explore the effect of substituent on the distal aryl rings of **43a** and **43b** (Kolodziej et al. 2010a). Compounds having *N*-aryl piperazine α-sulfone moiety failed to show any measurable potency for MMP-1 ($IC_{50} > 1000$ nM) but had 1000 times MMP-13 selectivity over MMP-1. *N*-aryl piperazines (**44a** and **44b**) had nanomolar potency for MMP-13 and -2 but moderate selectivity for the former over the latter. Some of their derivatives were found equipotent. As compared to *ortho* and *meta* substituted derivatives of **46**, the *para*-substituted derivatives maintained high potency and selectivity for MMP-13.

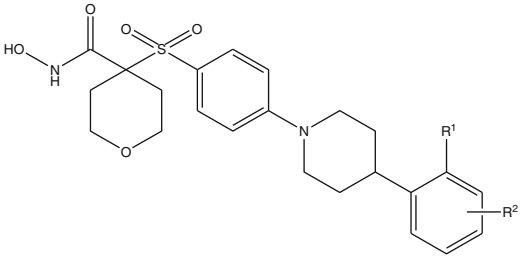


43a: Y = N; **43b**: Y = CH



44a: X = O; **44b**: X = N- *c*Pr

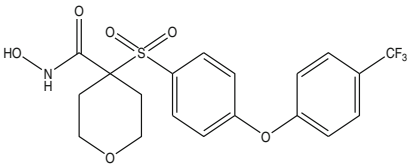
Kolodzeij et al. (2010b) derived another series of inhibitors (**45**) by varying the substituent at the aryl ring of **43b**. In order to boost the MMP-2 and -13 selectivity, they studied *para*-substituted analogs and found that the MMP-2 selectivity depended on the size of the substituent, with methoxy being optimal: H < Cl, OH < CH_3, CF_3 < OMe, OEt, and 4-F-C_6H_4. The decrease in affinity for MMP-13 was attributed to steric effects. The additional substituents like 2,3-(CH=CH)naphthyl, methyl, and methoxy showed increased MMP-2 potency and the *para*-substituted *N*-aryl piperazines showed superior MMP-13 potency.



45

Some orally active and MMP-1 sparing α-tetrahydropyranyl (α-THP) sulfone hydroxamates, such as **46**, and several α-piperidine sulfone hydroxamates (**47**) were synthesized and found to be potent inhibitors of MMP-2, -9, and -13 by Becker et al. (2010) with oral efficacy in inhibiting tumor growth in mice and left-ventricular hypertrophy in rats and in the bovine cartilage degradation explant system. In most cases, the α-piperidines exhibited greater exposure than the α-THP analogs. An analog of **47** (R = methoxyethyl; SC-78080/SD-2590) was selected for development toward the initial indication of cancer, while its another analog

(R = cyclopropyl; SC-77964) and **46** (SC-77774) were identified as backup compounds.



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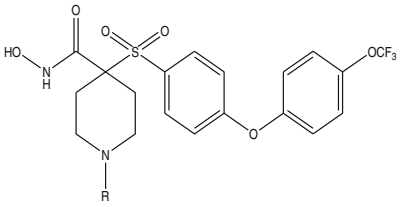
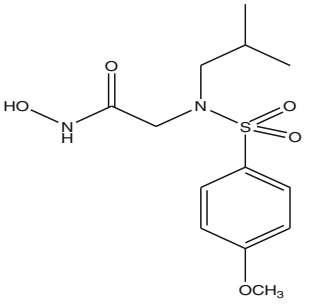
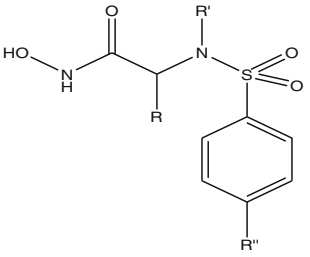


47

In *N*-arylsulfonyl-based MMPIs, the poor bioavailability is the major drawback for the development of this family of molecules. To enhance the water solubility, Attolino et al. (2010) applied a structure-based approach and performed structural analysis of **48** (NNGH) with MMP-12 to find that the *sec*-butyl residue was not directly involved in the binding with MMP. A new series of compounds (**49**) was then studied, where *sec*-butyl residue was replaced with hydroxamic acid moiety, to get water soluble potent inhibitors.



48 (NNGH)



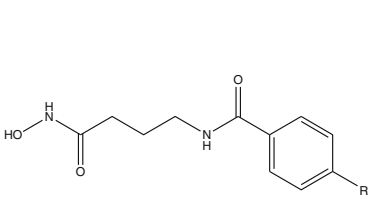
49

All the newly prepared analogs of **49** were evaluated, using NNGH as reference, against MMP-1, -7, -8, -9 -12, and -13 to find that all of them had low nanomolar K_i values for the MMPs tested except for MMP-1 and -7.

Analogs of **49** prepared with fluorine and biphenyl substituents instead of methoxy group to compliment the characteristic shape of the S1′ binding pocket were not found beneficial. The lack of favorable interactions of Arg214 with fluorine contributed toward the low affinity of the inhibitors and micromolar *Ki* value for MMP-1. A decrease in hydrophilicity of the compounds was found and thus the necessity of at least one hydroxyl group was felt.

5.6 N-Benzoyl Aminobutyric Acid Hydroxamates

Nakatani et al. (2006) studied a series of *N*-benzoyl 4-aminobutyric acid hydroxamate analogs (**50**–**54**) as inhibitors of MMP-1, -2, -3, and -9. Most of the compounds, like *N*-[4-(benzofuran-2-yl)benzoyl]-4-amino-4*S*-hydroxymethyl butyric acid hydroxamates, were found to be highly potent inhibitors of the gelatinases (MMP-2 and -9) as compared to the corresponding 2*S*- or 3*S*-hydroxy analogs.



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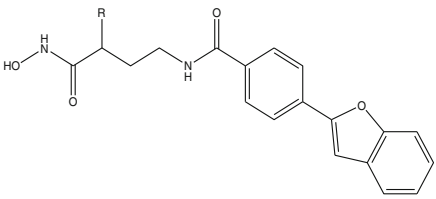

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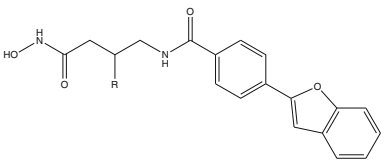

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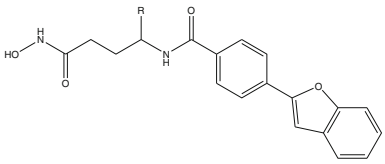

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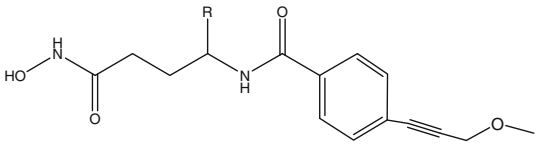
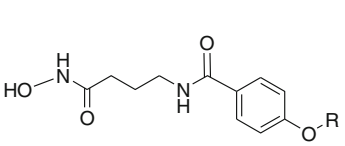


54

Ikura et al. (2006) performed chemical modification of the *N*-benzoyl residue of *N*-benzoyl γ-aminobutyric hydroxamic acids (**55**, **56**) by introducing electron-rich *para*-substituents and found it to be effective to increase the inhibitory activity of this class of MMPIs. Analogs having relatively more planar *N*-acyl residues demonstrated more potency. The three-dimensional arrangement of the two pharmacophores, hydroxamic acid and *N*-acyl residues, was optimized by chemical modifications of the γ-aminobutyric hydroxamic acid moiety (**50**) and this moiety was found as best spacer. All the compounds were evaluated for their inhibitory activity against MMP-1, -2, -3, and -9 and the *N*-benzoyl γ-aminobutyric hydroxamic acid was identified as a new chemical lead for MMP-2 and -9 inhibitions. Further chemical modification was focused on the 4-*N*-(4-methyl)benzoyl moiety, and a series of *N*-benzoyl γ-aminobutyric hydroxamic acids was prepared. As compared to 4-(*para*-alkylphenyl)benzoyl analogs, the 4-(*para*-substituted phenyl)benzoyl analogs were found to be stronger inhibitors. Introduction of electron-rich substituents (benzofuran-2-yl and *para*-chlorocinnamyl) at *para*-position of the *N*-benzoyl moiety was assumed to be

essential for strong activity. A secondary amide was found as a superior linkage compared to the ether or *N*-methyl amide with respect to the formation of hydrogen bonds with amino acid residues Pro238 and Leu181 in the S1′ pocket.



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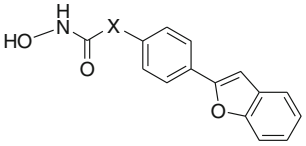
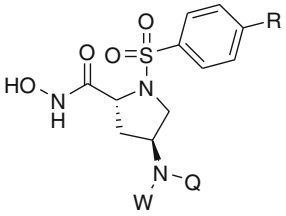


56

5.7 Aminoproline-Based Hydroxamates

A few series of hydroxamates (**57**–**60**) were reported as MMP inhibitors from an aminoproline scaffold by Natchus et al. (2000) where analogs of **57** were identified to have broad-spectrum activity with sub-nanomolar potency for some enzymes. Further modifications at the P1′ portion of this molecule with longer-chain aliphatic and aromatic substituents were found to affect both potency and selectivity within the MMP family. All compounds were assayed for the inhibition of MMP-1, -2, -3, -7, and -13.



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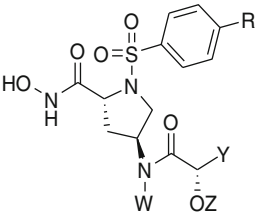

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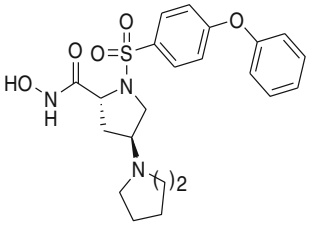

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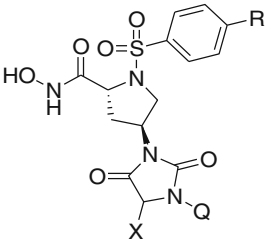

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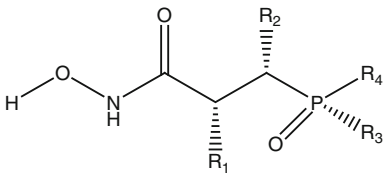
5.8 Aminopyrrolidine-Based Hydroxamates

A diverse family of aminopyrrolidine-based hydroxamate inhibitors were found to act as very potent inhibitors of MMP family with the exception of MMP-1 and -7 by Natchus et al. (2000). At the 4-position of the aromatic sulfonamides, long-

chain aliphatic groups were incorporated to enhance the selectivity against the shallow S1′ pocket of enzymes. The X-ray crystallography data of stromelysin-complex was used to explain the binding of aromatic sulfonamide structure into the S1′ pocket and the selectivity profile.

5.9 Phosphinamide/Phosphonamide-Based Hydroxamates

Pikul et al. (1999) studied some phosphinamide-based hydroxamates (**61**) where compounds having *R*-configuration at phosphorous were found to be potent inhibitors of MMP-1 and -3. The *S*-configuration was found inactive. A compound with $R_1 = CH_2CHMe_2$, $R_2 = CH_2Ph$, $R_3 = Me$, and $R_4 = Ph$ was found to be active against MMP-1 ($IC_{50} = 20.5$ nM) and MMP-3 ($IC_{50} = 24.4$ nM) where R_4-substituent could play key role in binding with S1′ pocket of the enzymes. The analysis of binding interactions indicated the involvement of Leu164, Ala165, Glu202, and Val163 residues of the enzymes.



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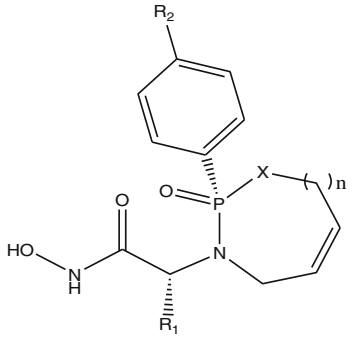
Some cyclophosphinamide- and cyclophosphonamide-based hydroxamates (**62**) were designed by altering the phosphorous substituent interacting with S1′ pocket and evaluated as potent MMPIs (Sorensen et al. 2003). The SAR conclusions were in accordance with those of Pikul et al. (1999) confirming the essential requirement of *R*-configuration of phosphorous atom and α-carbon. The 7-membered cyclophosphonamide and unsaturated 6-membered cyclophosphinamide hydroxamates were among the most potent inhibitors of MMP-1, -3, and -9. The proposed binding mode at MMP-3 has suggested interactions with Ala165, Leu164, Asn162, and Val163 as well as affinity of R_2-substituent toward S1′ pocket.



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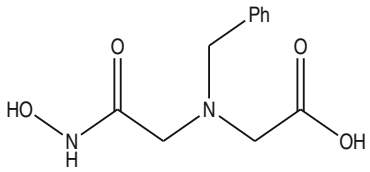
5.10 Non-Peptidyl Hydroxamates

A novel class of non-peptidyl hydroxamates, i.e., derivatives of *N*-aryl-iminodiacetic acid (IDA) (**63–65**) has been recently reported by Marques et al. (2006). To further improve the potency and selectivity versus MMP-2 and -13, some structural modifications were carried out to get new MMP-1/MMP-14-sparing hydroxamates inhibitors (Santos et al. 2006). As the specificity of MMP inhibition is correlated with the interactions at the S1′ pocket of the enzyme, the alkylaryl/sulfonylaryl substituents were added at the nitrogen and the carboxylic moiety was replaced by an amide chain.



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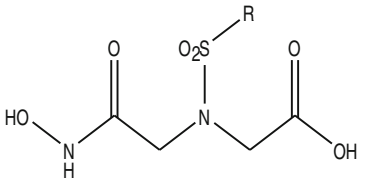

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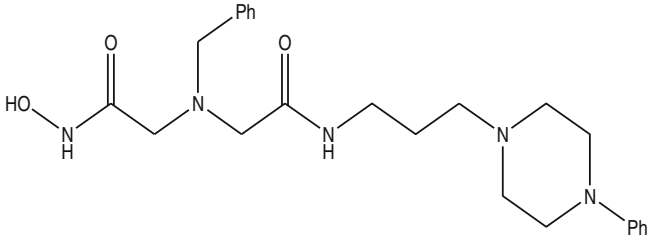
Among the sulfonamide analogs (**64**), the *para*-methoxybenzene, biphenyl, and *para*-phenoxybenzene showed good inhibitory potency against MMP-2, -7, -8, -9, -13, and -14. The *para*-phenoxybenzene analog was observed as most potent (IC_{50} = 1–30 nM) and the order of activity was as: MMP-2 > MMP-13 > MMP-9 > MMP-8 > MMP-16 > MMP-14. The authors concluded that the lipophilic, electrostatic, and steric properties are liable toward MMPI potency and selectivity. Also the sulfonyl group at the nitrogen is important which permits its oxygen to form H–bonds with Leu164 and Ala165 (MMP-2) and directs the lipophilic groups in the S1′ pocket.



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6 Conclusion

In conclusion, these SAR studies have indicated the following:

(1) The greatest potency with the MMP inhibitors can be associated with their ability to interact with S1, S1′, and S2′ subsites.

(2) S1′ differs most among the MMPs and a certain degree of specificity can be achieved by varying the P1′ residue of the inhibitors.
(3) Introduction of larger P1′ substituents generally gives greater specificity for MMP-2 and MMP-9.
(4) The P1′ substituent should preferably be a long side chain for the binding with MMP-2, MMP-3, and MMP-9.

In a recent article, Gupta and Patil (2012) have pointed out that the main subsites in MMPs for substrate recognition are the specificity pocket S1′ and, to a lesser extent, S2. The specificity pocket S1′ originates immediately to the right of catalytic Zn^{2+} ion and considerably differs in size and shape among the various MMPs. Due to this variation in size and shape, S1′ pocket offers selective inhibition of MMPs. The rough classification of S1′ specificity pockets according to the shape and size and the flexibility can aid in the development of selective MMP inhibitors. Because of the variation in the structure of S1′ pocket, modification of the P1′ can be used to introduce substrate specificity. The P1′–S1′ interaction is the main determinant for the affinity of inhibitors and the cleavage position of peptide substrates.

Several quantitative SARs (QSARs) on MMP inhibitors have been carried out. In a recent comprehensive review on QSAR studies on zinc-containing metalloproteinase inhibitors, Gupta (2007) concluded that in addition to binding with the catalytic Zn^{2+}, the MMP inhibitors may also have hydrophobic, steric, and electrostatic interactions with the enzymes that may provide them better potency. Verma and Hansch (2007) also came to the same conclusion from their QSAR studies on some series of hydroxamic acids acting as MMP inhibitors. Some molecular modeling studies have visualized these interactions (Matter et al.1999; Matter and Schwab 1999; Tsai and Lin 2004). The SAR studies presented here also indicated these types of interactions between the inhibitors and various MMPs.

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