Design, Synthesis, and Biological Evaluation of Potent Thiazine- and Thiazepine-Based Matrix Metalloproteinase Inhibitors

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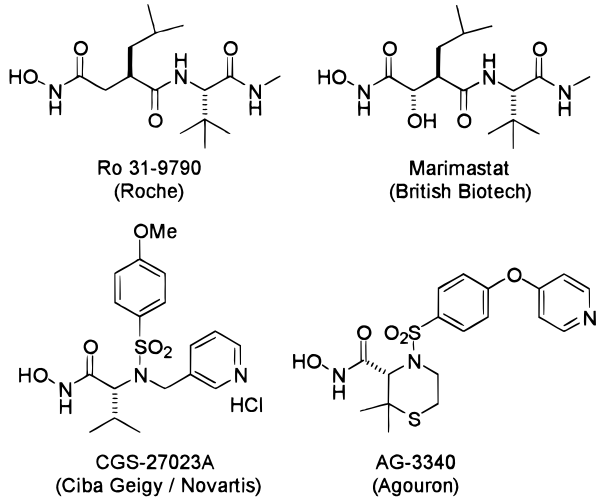
The synthesis and enzyme inhibition data for a series of thiazine- and thiazepine-based matrix metalloproteinase (MMP) inhibitors are described. The thiazine- and thiazepine-based inhibitors were discovered by optimization of hetererocyclic sulfonamide-based inhibitors. The most potent series of inhibitors was obtained by modification of the amino acid D-penicillamine. This amino acid provides a *gem*-dimethyl group on the thiazine or thiazepine ring which has a dramatic effect on the in vitro potency of this series. In particular, the sulfide **4a** and the sulfone **5a** were potent, broad-spectrum inhibitors of the MMPs with IC_{50}'s against MMP-1 of 0.8 and 1.9 nM, respectively. The binding mode of this novel thiazepine-based series of MMP inhibitors was established based on X-ray crystallography of the complex of stromelysin and **4a**.

Introduction

The matrix metalloproteinases (MMPs) are a structurally related class of enzymes that are responsible for the metabolism of the extracellular matrix proteins.[1,2] Members of this family, which include the collagenases, stromelysins, and gelatinases, are involved in the normal tissue remodeling processes such as wound healing, angiogenesis, and pregnancy. In these physiological processes the MMP activity is tightly regulated. The aberrant expression of these zinc- and calcium-dependent enzymes has been linked to the accelerated breakdown of connective tissues associated with pathological disease states including arthritis,[3] tumor invasion and metastasis,[4−7] periodontal disease,[8] and multiple sclerosis.[9−11] The MMPs and the inhibition of these enzymes have therefore become attractive targets for structure-based drug design.[12−15]

At the time we began to work in the field, few articles or patents had been published which described the design and synthesis of cyclic, sulfonamide-based inhibitors. Previous work in the field had primarily been focused on the development of acylic based MMP inhibitors (marimastat,[15] Ro 31-9790,[16] and CGS-27023A[17]). Our interest was in the design of molecules which possess some conformational rigidity,[18] possibly leading to increased in vitro potency and enhanced pharmacological properties. This structural rigidity could be introduced by the addition of a linker group (or ring) between the sulfonamide nitrogen atom and the C-2 carbon on the amino acid. An investigation of heterocyclic based sulfonamides was therefore undertaken with the goal to discover potent cyclic small molecule inhibitors of the MMPs. Recently, articles have been published which describe the design, synthesis, and SAR of heterocyclic inhibitors.[19] In addition, Agouron Pharmaceuticals is developing the thiazine analogue AG-3340 (Chart 1) as a disease-modifying agent for the treatment of cancer.[20] This manuscript provides an account of the discovery of a novel series of MMP inhibitors and describes the synthesis, initial structure−activity relationship (SAR) studies, and in vitro activity of this series of compounds.

Chart 1. Selected MMP Inhibitors



Chemistry

Synthesis of the thiazine- and thiazepine-based inhibitors was accomplished using one of two methods. In the first method, the methyl ester of D-penicillamine was allowed to react with 3-bromopropanol or 2-bromoethanol in the presence of DBU in DMF (Scheme 1). The resulting sulfide amino ester was then treated with the appropriate sulfonyl chloride and triethylamine to afford the desired sulfonamide **1** or **6**. Ring closure of the sulfonamide intermediate to produce the thiazepine **2** or thiazine **7** was accomplished under Mitsunobu[21] conditions with diethyl azodicarboxylate and triphenylphosphine. Hydrolysis of the methyl ester with lithium iodide/pyridine provided the carboxylic acids **3** and **8**.[22] The carboxylic acid was then treated with oxalyl chloride and DMF to generate the acid chloride in situ which was then treated with hydroxylamine to afford the hydroxamic acids **4** and **9**. The corresponding sulfones

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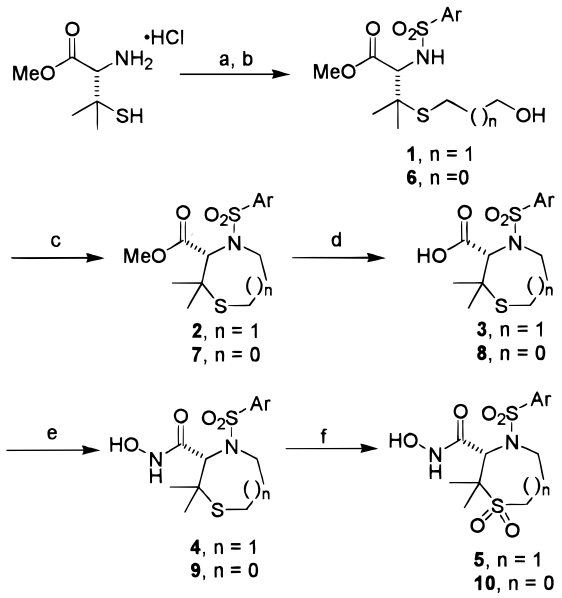
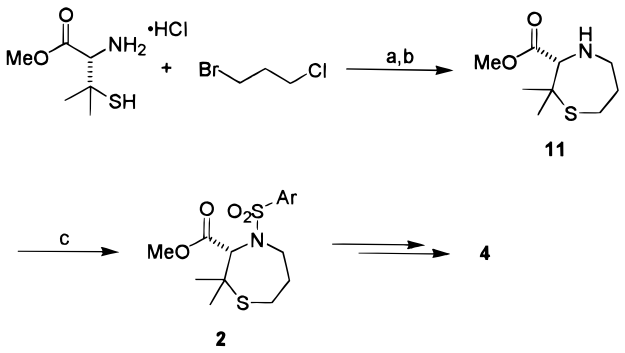
Scheme 1. Procedure A[a]



[a] Reagents and conditions: (a) 1,8-diazabicyclo[5.4.0]undec-7-ene (2 equiv), $Br(CH_2)_3OH$ ($n = 1$) or $Br(CH_2)_2OH$ ($n = 0$), DMF, 0 °C; (b) $ArSO_2Cl$, Et_3N, 1,4-dioxane, water; (c) diethyl azodicarboxylate, Ph_3P, THF; (d) LiI, pyridine, reflux; (e) 1. oxalyl chloride, DMF, CH_2Cl_2, 2. NH_2OH, water, THF; (f) CH_3CO_3H, $CHCl_3$.

Scheme 2. Procedure B[a]

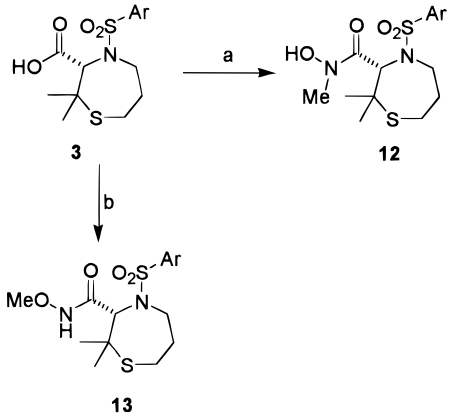


[a] Reagents and conditions: (a) 1,8-diazabicyclo[5.4.0]undec-7-ene (2 equiv), DMF, 0 °C; (b) 1,8-diazabicyclo[5.4.0]undec-7-ene (1 equiv), DMF, 80 °C; (c) $ArSO_2Cl$, 4-methylmorpholine, $CHCl_3$, reflux.

5 and **10** could be readily prepared by treatment of the hydroxamic acid with peracetic acid in chloroform. The hydroxamic acids were obtained as crystalline compounds which could be purified by recrystallization from the appropriate solvent.

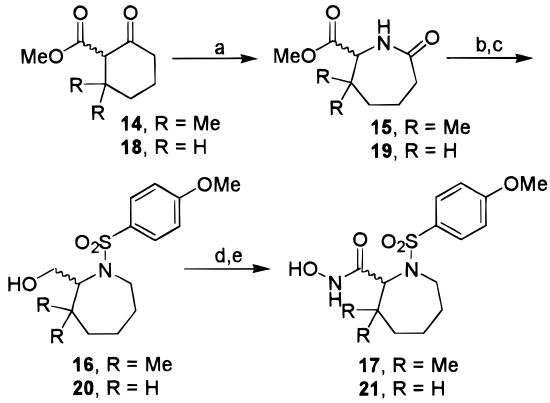
In the second method, the thiazepine ring was prepared in one step from the methyl ester of D-penicillamine and 3-bromo-1-chloropropane (Scheme 2). The penicillamine methyl ester was allowed to react with the alkyl bromide in the presence of DBU to produce the intermediate chloropropyl sulfide. The addition of 1 more equiv of DBU and then heating the mixture afforded the thiazepine **11**. The thiazepine methyl ester was then treated with the corresponding sulfonyl chloride and *N*-methylmorpholine to produce the desired sulfonamide. This method provided the desired sulfonamides in high yield, although the reaction of the corresponding sulfonyl chloride with the secondary amine was extremely slow. The remaining transformations leading to the hydroxamic acids were performed in a manner analogous to that described in Scheme 1.

Scheme 3[a]



[a] Reagents and conditions: (a) 1. oxalyl chloride, DMF, CH_2Cl_2, 2. MeNHOH, water, THF; (b) 1. oxalyl chloride, DMF, CH_2Cl_2, 2. NH_2OMe, water, THF.

Scheme 4[a]

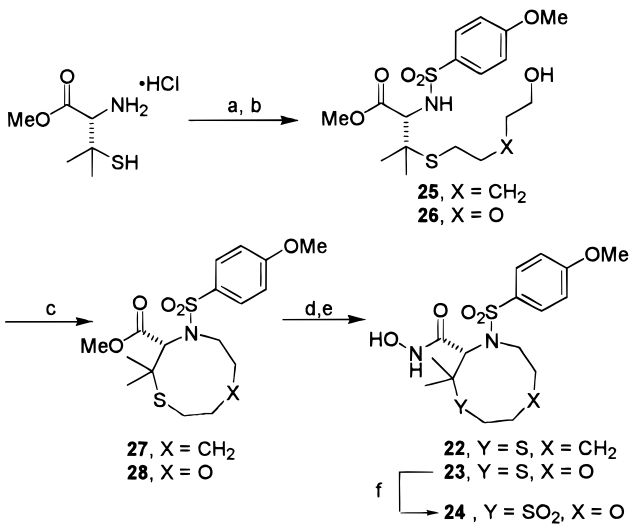


[a] Reagents and conditions: (a) NaN_3, $MeSO_3H$; (b) $LiAlH_4$; (c) 4-$MeOPhSO_2Cl$, Et_3N, dioxane, water; (d) Jones reagent, acetone; (e) 1. oxalyl chloride, DMF, CH_2Cl_2, 2. NH_2OH, water, THF.

The carboxylic acids could also be converted to the corresponding *N*-methyl- and *O*-methylhydroxamide derivatives. The carboxylic acid **3** was treated with oxalyl chloride to generate the acid chloride intermediate which was subsequently treated with either *N*-methyl- or *O*-methylhydroxylamine to produce **12** or **13**, respectively (Scheme 3).

The azepine **17** was synthesized in racemic form as shown in Scheme 4. This compound was prepared to assess the importance of the sulfur atom in the thiazepine ring for enzyme inhibition. Ring expansion via Schmidt rearrangement of an appropriately substituted β-keto ester appeared to be the most appealing route to this molecule. The Schmidt rearrangement was carried out with the keto ester **14**[23] by treatment with methanesulfonic acid followed by sodium azide to afford amide **15**.[24] The amide was reduced with lithium aluminum hydride to afford the amino alcohol which was subsequently treated with 4-methoxyphenylsulfonyl chloride and triethylamine to generate sulfonamide **16**. Oxidation of the primary alcohol with the Jones reagent provided the carboxylic acid which could be transformed to the desired hydroxamic acid **17** by treatment with oxalyl chloride followed by the addition of hydroxylamine. This methodology was also used to prepare the corresponding azepine **21**.

Scheme 5[a]



[a] Reagents and conditions: (a) 1,8-diazabicyclo[5.4.0]undec-7-ene (2 equiv), $Cl(CH_2)_5OH$ (for **25**) or $Cl(CH_2)_2O(CH_2)_2OH$ (for **26**), DMF, 0 °C; (b) 4-CH_3OPhSO_2Cl, Et_3N, 1,4-dioxane, water; (c) diethyl azodicarboxylate, Ph_3P, THF; (d) LiI, pyridine, reflux; (e) 1. oxalyl chloride, DMF, CH_2Cl_2, 2. NH_2OH, water, THF; (f) CH_3CO_3H, $CHCl_3$.

Large sulfur-containing heterocycles were prepared including the thiazonine **22** and the oxathiazonine **23** as shown in Scheme 5. The D-penicillamine methyl ester was treated with DBU and the corresponding alkyl chloride to provide the intermediate sulfide which was subsequently converted to the 4-methoxyphenylsulfonamide (**25** or **26**) by treatment with 4-methoxyphenylsulfonyl chloride and triethylamine. Mitsunobu cyclization produced the thiazonine (**27** or **28**) in moderate yield. The methyl ester was removed with lithium iodide in refluxing pyridine to give the carboxylic acid. Treatment of the carboxylic acid with oxalyl chloride followed by the addition of hydroxylamine yielded the desired hydroxamic acid (**22** or **23**). Oxidation of the oxazathiazonine to the corresponding sulfone **24** was accomplished by treatment with peracetic acid.

Hydroxyl- and alkoxyl-substituted thiazepines were synthesized as shown in Scheme 6. The synthesis begins with the addition of (*S*)-4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane[25] to D-penicillamine in the presence of dilute sodium hydroxide. Addition of 4-methoxyphenylsulfonyl chloride to the amino acid followed by treatment of the acid with ethereal diazomethane generated the methyl ester **29**. Conversion of **29** to the corresponding diol **30** was achieved by hydrolysis with dilute HCl. Differential protection of the diol was accomplished by the addition of *t*-$BuMe_2SiCl$ and triethylamine to produce the silyl ether. The secondary alcohol was then protected with MOMCl to give **31**. Removal of the silyl ether with fluoride provided primary alcohol **32** which was subjected to Mitsunobu cyclization conditions to give the thiazepine **33**. The methyl ester was hydrolyzed with LiI in pyridine, and the resulting carboxylic acid was treated with oxalyl chloride followed by hydroxylamine to afford the desired hydroxamic acid **34**. Oxidation of the sulfide to the sulfone and concomitant removal of the MOM group was accomplished by treatment with peracetic acid to generate **35**.

The thiazepine-based hydroxamic acids **36a** and **36b** containing an aryl substituent on the thiazepine ring were synthesized by a modification of procedure A (Scheme 1) from the corresponding amino acid derivative and (*R*)- or (*S*)-3-chloro-1-phenyl-1-propanol.

Results and Discussion

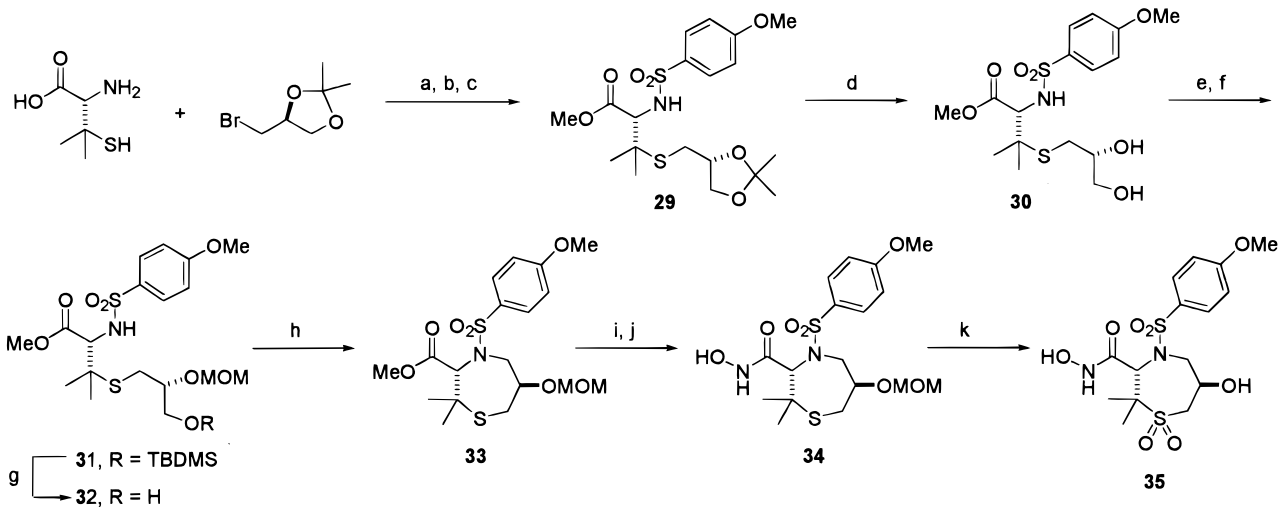
Development of the Heterocylic Based MMP Inhibitors. 1. Effect of Ring Size and Ring Heteroatom. All compounds were tested in vitro for the inhibition of truncated collagenase-1 (MMP-1),[26] stromelysin (MMP-3),[27] matrilysin (MMP-7),[26] and collagenase-3 (MMP-13).[26] Selected molecules have also been tested for inhibition of gelatinase-A (MMP-2),[26] neutrophil collagenase (MMP-8),[26] gelatinase-B (MMP-9),[26] and MT-MMP-1.[28] Initially, the effect of both ring size and presence of a ring heteroatom on enzyme inhibition was examined (Table 1). The inhibitors based on either the six- or seven-membered rings were quite potent against collagenase-1 (MMP-1) and stromelysin-1 (MMP-3). The corresponding five-membered proline- and cysteine-based inhibitors were determined to be almost 1 order of magnitude less potent than the larger rings. Because of the lower potency observed with the five-membered heterocycles, we chose to concentrate our efforts on the six- and seven-membered heterocycles.

The presence of a ring heteroatom in both the six- and seven-membered series did not significantly influence the potency or selectivity of the inhibitor (compare compounds **39**−**41**). In the six-membered ring series, substitution of the ring carbon with either an oxygen or sulfur atom had only a negligible effect on enzyme inhibition. The piperazine-based inhibitor (compound **43**, substitution with −NH) was determined to be somewhat less potent, although it has been observed that further substitution of the ring nitrogen in the piperazine series can lead to a significant increase in potency.[29] The results obtained with the sulfide **41** and the sulfone **42** were somewhat surprising. Oxidation of the sulfur atom in compound **41** to the corresponding sulfone **42** led to a significant decrease in potency.

Further examination of the sulfur-based inhibitors was initiated because of the ease of synthesis of these compounds and the ready availability of starting materials in the correct D-configuration for this series.[30]

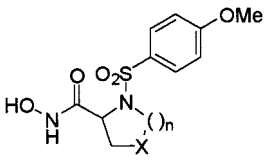
2. Effect of C-2 *gem*-Dimethyl Group on in Vitro Inhibition. When we began to work in the area of heterocyclic MMP inhibitors, we proposed that a *gem*-dimethyl group, when introduced adjacent to the hydroxamic acid functionality, may reduce the potential for metabolic degradation of the hydroxamic acid. It was hypothesized that steric shielding of the hydroxamic acid group could prevent or hinder this metabolic pathway. An examination of the effect a C-2 *gem*-dimethyl group might have on in vitro potency was undertaken. After installation of the *gem*-dimethyl group on the heterocyclic inhibitors, a dramatic increase in potency was observed in both the thiazine (six-membered ring) and thiazepine (seven-membered ring) series (compare values in Table 2 versus Table 1). The thiazine-based inhibitors containing the *gem*-dimethyl group were extremely potent inhibitors of both MMP-1 and MMP-3. Almost a 2 orders of magnitude increase in potency was observed against MMP-1 with the addition of the *gem*-dimethyl group (compare compound **41**, Table 1, with compound **9**, Table 2). A significant

Scheme 6[a]



[a] Reagents and conditions: (a) 2 N NaOH, EtOH; (b) 4-MeOPhSO$_2$Cl, Et$_3$N, 1,4-dioxane, water; (c) CH_2N_2, Et$_2$O; (d) 1 N HCl, THF; (e) TBDMSCl, Et$_3$N, CH_2Cl_2; (f) NaI, MOMCl, *i*-Pr$_2$EtN, DME; (g) *n*-Bu$_4$NF, THF; (h) diethyl azodicarboxylate, Ph$_3$P, THF; (i) LiI, pyridine, reflux; (j) 1. oxalyl chloride, DMF, CH_2Cl_2, 2. NH_2OH, water, THF; (k) CH_3CO_3H, $CHCl_3$.

Table 1. Effect of Ring Size and Ring Heteroatom on MMP Inhibition



			IC$_{50}$ (nM)[a]			
compd	n	X	MMP-1	MMP-3	MMP-7	MMP-13
37	1	CH_2	297	258	nd	nd
38	1	S	638	175	nd	nd
39	2	CH_2	23	14	313	0.5
40	2	O	49.5	5.8	nd	1.0
41	2	S	62	15	2070	1.0
42	2	SO_2	688	737	12848	18.4
43	2	NH	175	48	2390	1.7
21	3	CH_2	49	7.0	895	1.8
44	3	S	64	4.3	1102	1.9

[a] See Experimental Section for details of the enzyme assays. nd, not determined.

increase (at least 1 order of magnitude) in potency was also observed against MMP-3 and MMP-7 when the *gem*-dimethyl group was introduced. Interestingly, the influence of the *gem*-dimethyl group on the inhibition of MMP-13 was much less significant. The effect on in vitro inhibition was also observed in the sulfone series (compare compound **42**, Table 1, with compound **10**, Table 2). The sulfone **10** with the *gem*-dimethyl group was still an extremely potent inhibitor of MMP-1 and MMP-3, although it was significantly less potent than the parent thiazine **9**. It is readily apparent that the *gem*-dimethyl group has a dramatic effect on the potency of this series.

The thiazepines containing the C-2 *gem*-dimethyl group were determined to be as potent inhibitors of both MMP-1 and MMP-3 as the corresponding thiazine-based compounds. The major disparity between the thiazine- and thiazepine-based inhibitors was observed upon oxidation of the ring sulfur to the corresponding sulfone. Oxidation of the ring sulfur in the thiazepine series did not result in any significant decrease in potency (compare thiazines **9** and **10** with thiazepines **4a** and **5a**). This result was especially gratifying, as metabolic oxidation of a sulfide to the corresponding sulfoxide and sulfone is a well-known process.[31] It was also determined that the sulfone analogues were significantly more water soluble than the corresponding sulfide analogues (compound **4a**, 0.1 mg/mL, and compound **5a**, 0.8 mg/mL, at pH 7.4). We chose to concentrate our studies on further elaboration of the thiazepine (seven-membered ring)-based inhibitors which retain almost all potency even when the ring sulfur has been oxidized.

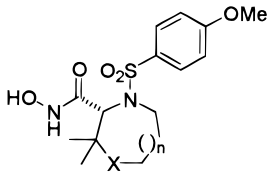
The corresponding azepine analogue **17** was also tested for in vitro inhibition. The in vitro profile of compound **17** was almost identical to the profile observed with the thiazepine **4a**. Apparently the sulfur atom does not significantly influence the potency of the molecule even in the *gem*-dimethyl series.

The nine-membered thiazonine **22** was prepared to determine if the enzyme active site could accommodate the large rings. This compound was determined to be as potent an inhibitor as the corresponding thiazepine **4a**.

The enantiomer of **4a**, *R*-**4a**, was prepared from L-penicillamine and tested for in vitro activity in order to examine the importance of amino acid configuration on enzyme inhibition. This compound (*R*-**4a**) was a very poor inhibitor of the MMPs, with potencies 3−4 orders of magnitude lower than that of the corresponding enantiomer **4a** (vide infra).

Structure of Stromelysin−Inhibitor Complex.[32] To better understand the binding interactions between the thiazepine based hydroxamic acids and the MMP

Table 2. Effect of *gem*-Dimethyl Group and Ring Size on MMP Inhibition



			IC_{50} (nM)[a]						
compd	n	X	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13
9	0	S	0.4	1.4	0.7	23	0.7	0.9	1.0
10	0	SO_2	13	14	18.5	nd	nd	nd	4.3
4a	1	S	0.8	2.7	0.7	30	1.4	1.9	0.9
***R*-4a**[d]	1	S	7780	2905	>10000	>10000	881	1390	2330
5a	1	SO_2	1.9	7.8	6.9	41	2.4	3.6	2.1
17	1	CH_2	2.4	1.4	3.3	18	1.9	0.5	nd
22	3	S	3.0	2.4	7.2	30	0.6	3.7	1.0
AG3340			4.9 (8.2)[b]	<0.4 (0.083)[b]	4.9 (0.27)[b]	91 (54)[b]	<0.4	<0.4	<0.4 (0.038)[b]
CGS27023A			49.5 (33)[c]	9.1 (20)[c]	17 (43)[c]	106	4.4	4.3 (8)[c]	4.3

[a] See Experimental Section for details of the enzyme assays. nd, not determined. [b] K_i values reported for AG3340 are given in parentheses. [c] K_i values reported for CGS27023A are given in parentheses. [d] *R*-Enantiomer of **4a**.

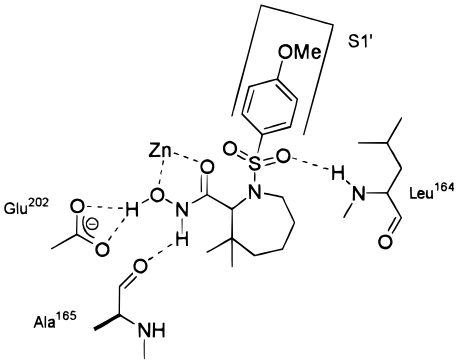


Figure 1. Binding interactions between **4a** and stromelysin.

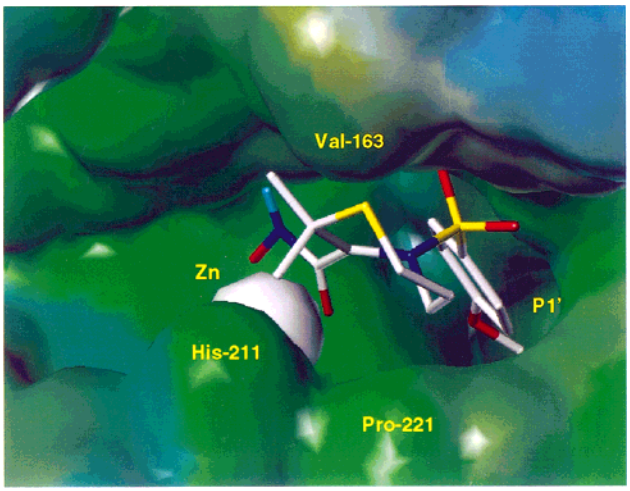
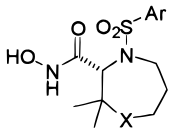


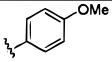
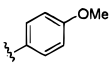
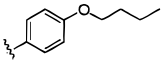
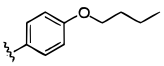
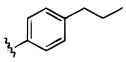
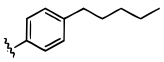
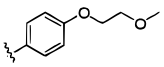
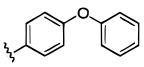
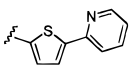
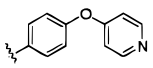
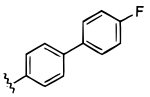
Figure 2. Structure of stromelysin−**4a** complex.

enzymes, we obtained a crystal of the truncated stromelysin−**4a** complex and solved its structure using the molecular replacement method. The catalytic site of stromelysin (MMP-3) with the bound inhibitor is shown in Figure 1. In general, interactions of the hydroxamic acid with stromelysin were consistent with those already reported in the literature.[18,33−35] The hydroxamic acid acted as a bidentate ligand with the two oxygen atoms in binding distance of 2.0 and 2.6 Å from the active site Zn^{2+} ion. The terminal OH oxygen and the nitrogen atom of the hydroxamic acid formed additional hydrogen bonds with the oxygen Oϵ2 (2.4 Å) of the carbonyl group of Glu-202 and the carbonyl group (2.7 Å) of Ala-165, respectively. The methoxyphenylsulfonamide group is clearly directed toward the S1′ site, and a hydrogen bond between Leu-164 and the sulfonamide oxygen may develop.

The most interesting feature of the enzyme−inhibitor interactions was revealed by inspection of the thiazepine ring. The thiazepine was oriented in a pseudo-chair conformation with the ring sulfur and one of the methyl groups directed toward Val-163. It is clear from inspection of the crystal structure that near the S2′ site, the inhibitor-binding cleft is large and relatively open. This cleft can accommodate P2′ groups of various sizes, which may explain the flat SAR observed after modification of the ring size and adding substituents to the thiazepine ring. Some of the side chains at this site vary among the different MMPs, but Pro-221 which is closest to the P2′ group is conserved among all the MMPs. The

Table 3. In Vitro Profile of Thiazepine MMP Inhibitors



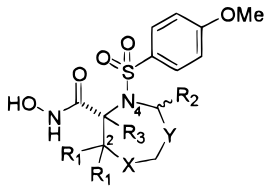
			IC_{50} (nM)[a]				
compd	X	Ar	MMP-1	MMP-2	MMP-3	MMP-7	MMP-13
4a	S		0.8	2.7	0.7	30	0.9
5a	SO_2		1.9	7.8	6.9	41	2.1
4b	S		0.7	6.8	10	17	1.3
5b	SO_2		1.2	20	90	79	2.7
4c	S		0.5	24	88	354	9.2
4d	S		18	1.0	6.6	nd	2.3
5d	SO_2		19	1.2	2.7	27	0.4
4e	S		22	35	46	637	7.5
4f	S		61	nd	25	330	2.1
4g	S		42	11.4	17	509	5.6
4h	S		2.3	nd	11	16	<0.4
4i	S		1.0	1.0	1.1	170	<0.2
4j	S		5.7	<0.4	6.3	105	<0.4
4k	S		2.9	1.3	6.5	<100	<1.0

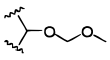
[a] See Experimental Section for details of the enzyme assays. nd, not determined.

thiazepine ring reaches close to the Pro-221 ring structure in the observed crystal structure. The stronger hydrophobic interaction that results probably contributes to increased potency with this series, and this interaction with Pro-221 is conserved for all MMPs. The high potency observed with the thiazepine series may also be influenced by a second strong hydrophobic interaction between one of the methyl groups and Val-163.

The significant reduction in potency observed with compounds derived from L-penicillamine (see compound *R*-**4a**, Table 2) was quite surprising and deserves further comment. The inhibition of the MMPs with acyclic L-amino acid-derived sulfonamides has previously been described by Ciba (Novartis).[17] These inhibitors were observed to be approximately 2 orders of magnitude less potent than the corresponding compounds derived from D-amino acids. When the thiazepine-based inhibitors were prepared from L-penicillamine, almost a 4 orders of magnitude decrease in potency was observed. The lack of potency observed with the L-penicillamine-derived analogues is likely due to poor interactions between the hydroxamic acid group and the active site zinc atom. The thiazepines which possess the L-configuration at the α-carbon would not be well-accommodated in the active site (see Figure 2). Due to these unfavorable interactions, the pseudo-chair structure observed in Figure 2 is much more difficult to adopt with the L-configured thiazepines, thus requiring significant reorganization of the enzyme and substrate for maximal inhibition to occur. The influence of configuration on inhibitor potency may be less significant with the acyclic

Table 4. In Vitro Profile of Thiazepine MMP Inhibitors



						IC_{50} (nM)[a]				
compd	R_1	X	Y	R_2	R_3	MMP-1	MMP-2	MMP-3	MMP-7	MMP-13
4a	Me	S	$-CH_2-$	H	H	0.8	2.7	0.7	30	0.9
34	Me	S		H	H	1.0	1.8	1.0	38	1.4
35	Me	SO_2		H	H	1.9	5.2	7.3	nd	1.3
23	Me	S	$-CH_2OCH_2-$	H	H	<1.0	3.5	0.7	<100	0.2
24	Me	SO_2	$-CH_2OCH_2-$	H	H	1.9	nd	45	183	3.3
36a	Me	S	$-CH_2-$	α-Ph	H	236	nd	26	54	137
36b	Me	S	$-CH_2-$	β-Ph	H	271	nd	33	110	2.5
45	H	S	$-CH_2-$	H	Me	217	4.2	31	17651	4.0

[a] See Experimental Section for details of the enzyme assays. nd, not determined.

sulfonamides due to the conformational flexibility that these compounds already possess.

Effect of Sulfonamide Group on in Vitro Inhibition. The sulfonamide portion of the molecule and the influence of this group on enzyme inhibition were also examined (Table 3). The *p*-methoxyphenylsulfonamide **4a**, one of the first compounds we examined, was determined to be an extremely potent and broad-spectrum inhibitor. The corresponding sulfone analogue, **5a**, was also prepared and tested for in vitro activity. This compound possessed a broad spectrum of activity against all of the MMPs we tested including matrilysin (MMP-7) and MT1-MMP[36] (MMP-14, IC_{50} 2.2 nM). Replacement of the *p*-methoxy group with a *p*-bromo substituent led to a significant shift in enzyme selectivity. Both the sulfide **4b** and the sulfone **5b** showed increased selectivity for MMP-1 over MMP-3. The *o*-methyl-*p*-bromophenylsulfonamide **4c** was found to be even more selective for MMP-1. Clearly, the bromophenylsulfonamides are well-tolerated by MMP-1, but the decrease in potency for MMP-3 remains hard to rationalize.

The results obtained with the *p*-butoxy substituent were somewhat surprising. On the basis of previous observations, compounds which possess a long P1′ substituent were expected to be more potent for MMP-3 while sparing MMP-1.[35] Instead, a slight decrease in potency was observed for both MMP-1 and MMP-3 with compounds **4d** and **5d**. The alkylated-phenylsulfonamides **4e** and **4f** were also potent inhibitors of the MMPs, but again, these compounds did not show any selectivity for MMP-3 over MMP-1. The aryl ethers **4h** and **4j**, the heterocyclic sulfonamide **4i,** and the biphenylsulfonamide **4k** were all broad-spectrum inhibitors and demonstrated extremely potent inhibition against MMP-13. The unexpectedly high potency of inhibitors with large P1′ groups toward MMP-1 has also been observed by Agouron Pharmaceuticals with the thiazine-based inhibitor AG3340.[37]

Based on the results obtained with the thiazepines, it is apparent that the addition of the *gem*-dimethyl group to the ring produces a potent, broad-spectrum inhibitor which is not significantly influenced by the P1′ (sulfonamide) region of the molecule. The addition of longer or bulkier substituents on the aryl ring (P1′ group) which are not usually tolerated by the shallow pocket metalloproteinases (MMP-1 and MMP-7) only had a moderate effect on enzyme selectivity with the thiazepine series.

SAR of the Thiazepine Ring. Modifications were made to the thiazepine ring to determine if further substitution of the thiazepine ring or a change in the ring size would alter the enzyme inhibition profile (Table 4). The first analogues tested (**34** and **35**) contain either a hydroxyl group or a methoxymethyl ether at C-6. Both of these compounds were potent broad-spectrum inhibitors and exhibited almost an identical inhibition profile to the parent compound **4a**. The nine-membered oxathiazonines **23** and **24** were also extremely potent MMP inhibitors. The effect of ring size

and the inclusion of another ring heteroatom had only a minimal effect on the enzyme inhibition profile. The introduction of a C-5 phenyl substituent resulted in significantly lower potency for MMP-1 and MMP-3. The β-phenyl compound **36b** was more potent than the corresponding α-phenyl inhibitor **36a** for MMP-13. Finally, the results obtained from in vitro testing of the methylcysteine analogue **45** indicated that introduction of a C-3 methyl group only had a modest effect on the inhibitory profile (compare compound **44**, Table 1, with compound **45**, Table 4).

Importance of the Hydroxamic Acid Moiety for in Vitro Activity. Modifications were also made to the hydroxamic acid portion of the molecule in order to determine if either a carboxylic acid or a substituted hydroxamic acid derivative would retain any in vitro activity. The corresponding carboxylic acids **3a** and **3h** were found to be inactive against all of the MMPs (IC_{50}'s $> 10\ \mu$M). The *N*-methylhydroxamic acids **12a** and **12h** and the *N*-methoxyhydroxamic acid derivative **13h** were also tested for in vitro inhibition. The *N*-methylhydroxamic acids were more than 3 orders of magnitude less potent than the parent hydroxamic acid. The *N*-methoxyhydroxamic acid **13h** was also completely inactive against the MMPs. These results clearly demonstrate the importance of the hydroxamic acid group in the thiazepine series for in vitro inhibition. Any modification of this group leads to a dramatic and almost complete loss of activity.

Conclusion

A potent series of thiazepine-based hydroxamic acid metalloproteinase inhibitors was discovered and optimized. The compounds which possess a *gem*-dimethyl group at C-2 were determined to be at least 1 order of magnitude more potent against MMP-1 (collagenase-1) than the corresponding dihydro analogues. A significant boost in potency was also observed against MMP-3 (stromelysin-1) when the *gem*-dimethyl group was added. The most potent inhibitors were readily prepared from the amino acid D-penicillamine which contains the requisite *gem*-dimethyl group. The compounds demonstrated broad-spectrum inhibition of the MMPs irrespective of the structure of the P1′ group. Even the large phenoxyphenyl- and butoxyphenylsulfonamides were potent inhibitors of MMP-1. Increasing the ring size and adding substituents to the thiazepine ring also did not result in any appreciable change in potency for the series. This broad-spectrum activity may be due to strong hydrophobic interactions of the thiazepine ring with Pro-221.

Experimental Section

General. All commercial chemicals and solvents are reagent grade and were used without further purification unless otherwise specified. The following solvents and reagents have been abbreviated: tetrahydrofuran (THF), ethyl ether (Et_2O), dimethyl sulfoxide (DMSO), ethyl acetate (EtOAc), dimethylformamide (DMF), methanol (MeOH). All reactions except those in aqueous media were carried out with the use of standard techniques for the exclusion of moisture. Reactions were monitored by thin-layer chromatography on 0.25-mm silica gel plates (60F-254, E. Merck) and visualized with UV light, iodine vapors, or 5% phosphomolybdic acid in 95% ethanol. Final compounds were typically purified either by flash chromatography on silica gel (E. Merck, 40−63 μm) or by preparative reverse-phase high-pressure liquid chromatography (RP-HPLC) using a Waters model 4000 Delta Prep instrument equipped with a Waters Symmetry preparative steel column (C-18, 19 mm × 300 mm) as the stationary phase. The mobile phase employed 0.1% aqueous trifluoroacetic acid with acetonitrile as the organic modifier. Linear gradients were used in all cases, and the flow rate was 20 mL/min. Analytical purity was assessed by RP-HPLC using a Waters 600 system equipped with a diode array spectrometer (λ range 200−400 nm). The stationary phase was a Waters Symmetry C-18 column (4.6 mm × 200 mm). The mobile phase employed 0.1% aqueous trifluoroacetic acid with acetonitrile as the organic modifier and a flow rate of 1.0 mL/min.

^{1}H NMR spectra were recorded on a Varian Unity-300 instrument. Chemical shifts are reported in parts per million (ppm, δ units). Coupling constants are reported in units of hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Low-resolution mass spectra (MS) were recorded on a Micromass Platform quadrupole mass spectrometer. Mass spectra were acquired in either the positive or negative ion mode under electrospray ionization (ESI). Combustion analyses were performed internally.

Human synovial proMMP-3 was obtained from Dr. Hideaki Nagase, University of Kansas Medical Center, Kansas City, KS. Human fibroblast proMMP-1, human MMP-9, and human recombinant MMP-7 catalytic domain were obtained from Dr. Howard Welgus, Jewish Hospital, St. Louis, MO. Human recombinant MMP-8 catalytic domain was obtained from Dr. Harald Tschesche, University Bielefeld, Bielefeld, Germany. Human recombinant proMMP-2 was purified from CHO cells as described below. Human recombinant truncated MMP-3 and truncated MMP-1 were purified from *E. coli* cells as described below. Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 was purchased from Bachem Bioscience, King of Prussia, PA. Phenoxyphenylsulfonyl chloride[38] and (pyrid-4-yl)oxyphenylsulfonyl chloride[39] were prepared following literature procedures.

Procedure A for Formation of Thiazepines 4a−4h. Methyl *N*-[(4-Methoxyphenyl)sulfonyl]-*S*-(2-hydroxypropyl)-D-penicillamine (1a). A solution of 2-bromopropanol (3.50 g, 24.1 mmol) in DMF (40 mL) was stirred at room temperature, and then a solution of D-penicillamine methyl ester hydrochloride (5.0 g, 25.1 mmol), 1,8-diazabicyclo[5.4.0]-undec-7-ene (7.64 g, 50.2 mmol, 2 equiv), and DMF (40 mL) was slowly added by dropwise addition over a 30 min period. The resulting mixture was stirred at room temperature overnight. The solvent was then removed to leave a thick oil. The oil was dissolved in dioxane (75 mL) and water (75 mL) and then triethylamine (6.32 g, 62.5 mmol, 2.5 equiv) followed by 4-methoxyphenylsulfonyl chloride (5.42 g, 26.3 mmol, 1.05 equiv) were added at room temperature. The resulting mixture was stirred for 18 h at room temperature and then acidified with 1 N HCl. The mixture was extracted with methylene chloride (2 × 250 mL) and the organic extracts were dried ($MgSO_4$) and then concentrated to an oil. Purification of the resulting methyl ester was accomplished by chromatography on silica gel using 1/1 hexane/EtOAc as the eluent. The desired product (8.0 g, 82%) was obtained as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, $J = 8.6$, 2 H), 6.88 (d, $J = 8.6$, 2 H), 5.62 (d, $J = 11$, 1 H), 3.82 (s, 3 H), 3.78 (d, $J = 11$, 1 H), 3.66 (m, 2 H), 3.40 (s, 3 H), 2.59 (br m, 2 H), 2.05 (br s, 1 H), 1.64 (m, 2 H), 1.36 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.13, 162.86, 130.69, 129.30, 113.89, 62.91, 60.81, 55.44, 51.91, 46.54, 31.31, 25.73, 24.40.

Methyl 4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethylhexahydro-1,4-thiazepine-3(*S*)-carboxylate (2a). The methyl ester **1a** (30.0 g, 76.6 mmol) in THF (400 mL) was stirred at room temperature and then triphenylphosphine (24.1 g, 91.9 mmol, 1.2 equiv) followed by diethyl azodicarboxylate (14.7 g, 84.3 mmol, 1.1 equiv) were added. The resulting solution was stirred at room temperature for 2 h. The solvent was removed; then the thick yellow oil was diluted with methylene chloride and silica gel (60 g) was added. The solvent was removed to

leave a white powder. This powder was placed upon a chromatography column and eluted with 8/2 hexane/EtOAc. The desired product (25.0 g, 87%) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.6, 2 H), 6.91 (d, J = 8.6, 2 H), 3.99 (m, 1 H), 3.83 (s, 3 H), 3.42 (m, 1 H), 3.38 (s, 3 H), 2.82 (br m, 1 H), 2.63 (m, 1 H), 2.22 (m, 1 H), 1.87 (m, 1 H), 1.61 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.94, 162.63, 130.83, 129.17, 113.67, 67.03, 55.38, 51.19, 46.93, 43.82, 31.45, 29.40, 26.18; MS (ESI) 374 (M^+), 391 (MNH_3^+).

4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylic Acid (3a). The methyl ester **2a** (26.7 g, 71.5 mmol) in pyridine (400 mL) was stirred at room temperature under an argon atmosphere. Lithium iodide (115 g, 858 mmol, 12 equiv) was added and the resulting solution was heated to reflux for 3 h. The reaction mixture was cooled to room temperature and then the solution was acidified with 1N HCl. The mixture was extracted with methylene chloride and then the organic extracts were dried (Na_2SO_4) and concentrated to an oil under reduced pressure. The oil was purified by column chromatography using 1/1 hexane/EtOAc as the eluent to provide the desired product (18 g, 70%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 8.7, 2 H), 6.93 (d, J = 8.7, 2 H), 3.88 (s, 3 H), 3.83 (m, 1 H), 3.64 (m, 1 H), 2.80 (br m, 2 H), 2.22 (m, 1 H), 1.90 (m, 1 H), 1.61 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.47, 162.75, 130.63, 129.38, 113.81, 67.44, 55.40, 47.04, 44.05, 31.29, 29.61, 26.42, 26.19; MS (ESI) 360 (M^+), 377 (MNH_3^+).

***N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4a).** The carboxylic acid **3a** (14.9 g, 41.6 mmol) in dichloromethane (200 mL) was stirred at room temperature and then oxalyl chloride (10.8 g, 85.2 mmol, 2.05 equiv) and DMF (3.04 g, 41.6 mmol) were added. The resulting solution was stirred at room temperature for 30 min. In a separate flask, hydroxylamine hydrochloride (11.6 g, 166 mmol, 4 equiv) in THF (50 mL) and water (10 mL) was stirred at 0 °C. Triethylamine (25.3 g, 249.6 mmol, 6 equiv) was added and the resulting solution was stirred at 0 °C for 15 min. The acid chloride solution was next added to the hydroxylamine solution at 0 °C and the resulting mixture was allowed to stir overnight at room temperature. The reaction mixture was next acidified with 1 N HCl and then extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated to a solid under reduced pressure. The solid was recrystallized from CH_3CN to provide a white powder (11.4 g, 73%): ^{1}H NMR (CD_3OD) δ 7.42 (d, J = 8.6, 2 H), 6.65 (d, J = 8.6, 2 H), 3.91 (s, 1 H), 3.56 (s, 3 H), 2.98 (m, 1 H), 2.52 (m, 1 H), 2.38 (m, 1 H), 1.85 (m, 1 H), 1.52 (m, 1 H), 1.22 (s, 3 H), 0.98 (s, 3 H); MS (ESI) 392 (MNH_3+), 375 (M^+). Anal. ($C_{15}H_{22}N_2O_5S_2$) C, H, N.

***N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*R*)-carboxamide (*R*-4a).** Following procedure A described above, the title compound was prepared from L-penicillamine as a white powder. Anal. ($C_{15}H_{22}N_2O_5S_2$) C, H, N.

***N*-Hydroxy-4-[(4-bromophenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4b).** Following procedure A described above, 14.65 g (36.0 mmol) of carboxylic acid **3b** was converted to 13.2 g (87%) of the desired product **4b** (white powder, recrystallized from acetonitrile): ^{1}H NMR (DMSO-d_6) δ 10.10 (s, 1H) 7.73 (m, 4 H), 4.89 (s, 1 H), 4.65(br m, 1 H), 4.10 (s, 1 H), 3.35 (m, 2 H), 2.91 (br m, 1 H), 2.64 (br m, 1 H), 2.25 (m, 1 H), 1.89 (m, 1 H), 1.57 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 168.91, 138.08, 133.55, 130.00, 128.62, 65.38, 47.08, 44.59, 32.95, 30.44, 27.28, 26.74; MS (ESI) 423, 425 (M^+). Anal. ($C_{14}H_{19}BrN_2O_4S_2$) C, H, N.

***N*-Hydroxy-4-[(4-bromo-2-methylphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4c).** Following procedure A described above, 1.65 g (3.9 mmol) of carboxylic acid **3c** was converted to 1.35 g (75%) of the desired product **4c** (white powder, recrystallized from CH_3CN/H_2O): ^{1}H NMR ($CDCl_3$) δ 7.56 (m, 3 H), 4.18 (s, 1 H), 3.44 (m, 1H), 3.33 (s, 1 H), 2.81 (m, 3 H), 2.62 (m, 4 H), 2.19 (m, 1 H), 1.90 (m, 1 H), 1.58 (s, 3 H), 1.34 (s, 3 H): ^{13}C NMR ($CDCl_3$) δ 167.04, 142.64, 138.79, 136.66, 131.05, 130.47, 128.67, 65.22, 45.60, 33.19, 30.36, 27.12, 26.99, 20.62; MS (ESI) 437, 439 (M^+), 454, 456 (MNH_3^+). Anal. ($C_{15}H_{21}BrN_2O_4S_2$) C, H, N.

***N*-Hydroxy-4-[(4-butoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4d).** Following procedure A described above, 1.65 g (4.15 mmol) of carboxylic acid **3d** was converted to 1.4 g (80%) of the desired product **4d** (white powder, recrystallized from CH_3CN/H_2O): ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 8.6, 2 H), 6.98 (d, J = 8.6, 2 H), 4.88 (s, 1 H), 4.22 (s, 1H), 4.01 (m, 3 H), 3.32 (m, 2 H), 2.84 (m, 1 H), 2.63 (m, 1H), 2.22 (m, 1 H), 1.78 (m, 3 H), 1.56 (m, 3 H), 1.45 (m, 2 H), 1.13 (m, 3 H), 1.01 (m, 3 H): ^{13}C NMR ($CDCl_3$) δ 170.12, 167.89, 164.57, 130.40, 115.72, 69.19, 65.05, 44.52, 32.85, 32.25, 30.24, 27.15, 26.53, 20.21, 14.10; MS (ESI) 417 (M^+), 434 (MNH_3^+). Anal. ($C_{18}H_{29}N_2O_5S_2$·0.5 H_2O) C, H, N.

***N*-Hydroxy-4-[[4-(2-methoxyethoxy)phenyl]sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4 g).** Following procedure A described above, 4.27 g (10.6 mmol) of carboxylic acid **3g** was converted to 3.57 g (80%) of the desired product **4g** (white powder, solid was triturated from toluene): ^{1}H NMR (DMSO-d_6) δ 10.76 (br s, 1 H), 8.91 (s, 1 H), 7.72 (d, J = 8.8, 2 H), 7.07 (d, J = 8.8, 2 H), 4.75 (m, 1 H), 4.19 (m, 2 H), 4.15 (s, 3 H), 3.68 (m, 2 H), 3.31 (s, 3 H), 3.13 (m, 1 H), 2.70 (m, 2 H), 2.03 (m, 1 H), 1.75 (m, 1 H), 1.45 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 165.08, 162.27, 131.54, 129.68, 115.44, 70.80, 68.09, 63.10, 58.87, 47.78, 43.22, 31.86, 30.03, 26.47, 26.24; MS (ESI) 419 (M^+), 436 (MNH_3^+). Anal. ($C_{17}H_{26}N_2O_6S_2$·H_2O) C, H, N.

4-[(4-Phenoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylic Acid (3h). Following procedure A described above, 5.03 g (11.5 mmol) of methyl ester **2h** was converted to 4.51 g (92%) of carboxylic acid **3h**: ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.8, 2 H), 7.42 (m, 2 H), 7.23 (m, 1 H), 7.01 (m, 4 H), 4.58 (s, 1 H), 3.84 (m, 1 H), 3.61 (m, 1 H), 2.83 (m, 1 H), 2.66 (m, 1 H), 2.20 (m, 1 H), 1.90 (m, 1 H), 1.61 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.36, 161.69, 155.40, 143.20, 133.06, 130.39, 129.94, 126.68, 125.10, 120.35, 117.71, 67.99, 47.49, 44.64, 31.78, 30.10, 26.84, 26.67; MS (ESI) 422 (M^+).

***N*-Hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4h).** Following procedure A described above, 0.40 g (0.95 mmol) of carboxylic acid **3h** was converted to 0.18 g (44%) of hydroxamic acid **4h**: ^{1}H NMR (DMSO-d_6) δ 10.88 (br s, 1 H), 8.90 (s, 1 H), 7.78 (d, J = 8.8, 2 H), 7.55 (m, 2 H), 7.25−7.05 (m, 7 H), 4.78 (m, 1 H), 4.12 (s, 1 H), 3.18 (m, 2 H), 2.62 (m, 2 H), 2.04 (m, 1 H), 1.78 (m, 1 H), 1.45 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 165.00, 161.30, 155.48, 133.09, 131.07, 130.04, 125.62, 120.82, 118.20, 63.20, 47.75, 43.48, 31.96, 30.04, 26.48, 26.25; MS (ESI) 437 (M^+). Anal. ($C_{20}H_{24}N_2O_5S_2$) C, H, N.

Procedure B for Formation of Thiazepines 4i−4k. Methyl 2,2-Dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylate (11). D-Penicillamine methyl ester (25.0 g, 125.2 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 38.1 g, 250.4 mmol, 2.0 equiv), and DMF (80 mL) were added to a solution of 3-bromo-1-chloropropane (20.7 g, 131.4 mmol, 1.05 equiv) in DMF (45 mL) at 0 °C. The mixture was added slowly over a 1-h period. The resulting mixture was heated to 80 °C and additional DBU (19.1 g, 125.2 mmol, 1 equiv) was added. The reaction was complete after 5 h at 80 °C. The reaction was cooled to room temperature and then poured into dilute sodium bicarbonate solution. The resulting mixture was extracted with EtOAc. The organic extracts were dried ($MgSO_4$) and then concentrated to an oil under reduced pressure. Purification of the oil was accomplished by chromatography on silica gel using 85/15 hexane/EtOAc as the eluent to provide 10.5 g (41%) of the desired product: ^{1}H NMR (DMSO-d_6) δ 3.73 (s, 3 H), 3.41 (s, 1 H), 3.31 (ddd, J = 2.8, 6.5, 14.2, 1 H), 2.88 (m, 2 H), 2.61 (ddd, J = 5.4, 5.4, 15.3, 1 H), 1.91 (m, 2 H), 1.42 (s, 3 H), 1.30 (s, 3 H); MS (ESI) 204 (M^+).

Methyl 4-[5-(Pyrid-2-yl)thienylsulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylate (2i). The thiazepine (2.0 g, 9.83 mmol) in chloroform (25 mL) was stirred at room temperature and then *N*-methylmorpholine (2.20 g,

21.6 mmol, 2.2 equiv), *N*,*N*-(dimethylamino)pyridine (25 mg), and 5-(pyrid-2-yl)thiophene-2-sulfonyl chloride (2.68 g, 10.3 mmol, 1.05 equiv) were added. The resulting mixture was heated to reflux for 5 days until almost no starting material remained. The reaction was cooled to room temperature and then poured into dilute sodium bicarbonate solution. The mixture was extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4) and then concentrated to an oil under reduced pressure. The oil was purified by chromatography on silica gel using 3/2 hexane/EtOAc as the eluent. The product (3.0 g, 72%) was obtained as a light yellow oil: ^{1}H NMR (DMSO-d_6) δ 8.59 (ddd, J = 1.0, 1.7, 4.9, 1 H), 7.79−7.66 (br m, 2 H), 7.52 (d, J = 3.9, 1 H), 7.49 (d, J = 4.0, 1 H), 7.25 (ddd, J = 1.1, 4.8, 7.4, 1 H), 4.60 (s, 1 H), 4.07 (ddd, J = 3.5, 12.0, 15.6, 1 H), 3.71 (m, 1 H), 3.49 (s, 3 H), 2.88 (m, 1 H), 2.72 (m, 1 H), 2.28 (m, 1 H), 1.95 (m, 1 H), 1.64 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 168.81, 151.03, 150.81, 149.76, 140.40, 136.86, 132.52, 123.29, 123.16, 118.97; MS (ESI) 427 (M^+).

4-[5-(Pyrid-2-yl)thienylsulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylic Acid (3i). The methyl ester (1.48 g, 3.47 mmol) was stirred with 6 N HCl (50 mL) at reflux for 16 h. The reaction mixture was cooled to room temperature and then neutralized to pH ~ 6 with 50% NaOH solution. The resulting yellow precipitate was filtered off and then washed with water. The solid was dried under vacuum to provide 1.20 g (84%) of the desired product.

***N*-Hydroxy-4-[5-(pyrid-2-yl)thienylsulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4i).** The carboxylic acid (1.10 g, 2.66 mmol) in dichloromethane (20 mL) was stirred at room temperature and then oxalyl chloride (0.41 g, 3.20 mmol, 1.2 equiv) was added. The resulting solution was stirred at room temperature overnight. In a separate flask, hydroxylamine (50% solution in water, 1.76 mL, 26.6 mmol, 10 equiv) in THF (7 mL) and *tert*-butyl alcohol (4 mL) were stirred at 0 °C. The acid chloride solution was next added to the hydroxylamine solution at 0 °C and the resulting mixture was allowed to stir 2 h at room temperature. The reaction mixture was poured into water and then extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated to an oil under reduced pressure. The oil was crystallized from CH_3CN to provide 0.65 g (57%) of the desired product as a white powder: ^{1}H NMR (DMSO-d_6) δ 9.79 (s, 1 H), 8.96 (s, 1 H), 8.59 (m, 1 H), 8.06 (m, 1 H), 7.93 (m, 1 H), 7.86 (d, J = 4.0, 1 H), 7.62 (d, J = 4.0, 1 H), 7.40 (ddd, J = 1.1, 5.0, 8.8, 1 H), 4.83 (m, 1 H), 4.19 (s, 1 H), 3.42 (m, 1 H), 2.63 (m, 2 H), 2.10 (m, 1 H), 1.92 (m, 1 H), 1.42 (s, 3 H), 1.22 (s, 3 H); MS (ESI) 428 (M^+). Anal. ($C_{17}H_{21}N_3O_4S_3$) C, H, N.

***N*-Hydroxy-4-[4-((pyrid-4-yl)oxy)phenylsulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4j).** Following procedure B described above, 2.74 g (6.47 mmol) of carboxylic acid **3j** was converted to 1.70 g (60%) of the desired hydroxamic acid **4j** as a white powder: ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1 H), 8.86 (s, 1 H), 8.57 (d, J = 6.0, 2 H), 7.88 (d, J = 8.6, 2 H), 7.25 (d, J = 8.6, 2 H), 7.04 (d, J = 6.0, 2 H), 4.76 (m, 1 H), 4.10 (s, 1 H), 3.23 (m, 1 H), 2.64 (m, 2 H), 2.04 (m, 1 H), 1.83 (m, 1 H), 1.44 (s, 3 H), 1.22 (s, 3 H); MS (ESI) 438 (M^+).

***N*-Hydroxy-4-[4-(4-fluorophenyl)phenylsulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (4k).** Following procedure B described above, 2.40 g (5.66 mmol) of carboxylic acid **3k** was converted to 1.20 g (48%) of the desired product **4k** as a white powder: ^{1}H NMR (DMSO-d_6) δ 10.80 (s, 1 H), 8.88 (s, 1 H), 7.86 (s, 4 H), 7.82 (m, 2 H), 7.36 (m, 2 H), 4.80 (m, 1 H), 4.22 (s, 1 H), 3.22 (m, 1 H), 2.64 (m, 2 H), 2.08 (m, 1 H), 1.83 (m, 1 H), 1.44 (s, 3 H), 1.22 (s, 3 H); MS (ESI) 439 (M^+). Anal. ($C_{20}H_{23}FN_2O_4S_2$) C, H, N.

General Procedure for Oxidation of Thiazepines to the Corresponding Sulfones 5a−5g. *N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide 1,1-Dioxide (5a). The hydroxamic acid **4a** (4.7 g, 12.55 mmol) was dissolved in chloroform (50 mL) at 0 °C in an ice bath. A solution of 32% peracetic acid (7.9 mL, 37.65 mmol, 3.0 equiv in acetic acid) was added and the mixture was then stirred at room temperature. An additional 3 equiv of 32% peracetic acid was added after 3 h and the resulting mixture was stirred overnight. Once the reaction was complete, the solvent was removed under reduced pressure. The resulting white solid was recrystallized with acetonitrile to provide a white powder: ^{1}H NMR (CD_3OD) δ 7.42 (d, J = 8.6, 2 H), 6.65 (d, J = 8.6, 2 H), 3.91 (s, 1 H), 3.56 (s, 3 H), 2.98 (m, 1 H), 2.52 (m, 1 H), 2.38 (m, 1 H), 1.85 (m, 1 H), 1.52 (m, 1 H), 1.22 (s, 3 H), 0.98 (s, 3 H); MS (ESI) 407 (M^+). Anal. ($C_{15}H_{22}N_2O_7S_2$) C, H, N.

***N*-Hydroxy-4-[(4-bromophenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide 1,1-Dioxide (5b).** Following the above procedure, the hydroxamic acid **4b** (4.2 g, 9.9 mmol) was converted to 4.1 g (91%) of the desired product **5b** (white solid, recrystallized from acetonitrile): ^{1}H NMR (DMSO-d_6) δ 10.10 (s, 1H), 7.78 (m, 4 H), 4.92 (s, 1 H), 4.59 (s, 1 H), 3.91 (m, 1 H), 3.74 (m, 1 H), 2.91 (br m, 1 H), 2.64 (br m, 1 H), 2.25 (m, 1 H), 1.89 (m, 1 H), 1.57 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 168.91, 138.08, 133.55, 130.00, 128.62, 65.38, 47.08, 44.59, 32.95, 30.44, 27.28, 26.74; MS (ESI) 455, 457 (M^+). Anal. ($C_{14}H_{19}BrN_2O_6S_2$) C, H, N.

***N*-Hydroxy-4-[(4-butoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide 1,1-Dioxide (5d).** Following the above procedure, the hydroxamic acid **4d** (0.50 g, 1.2 mmol) was converted to 0.44 g (88%) of the desired product **5d** as a white solid (recrystallized from acetonitrile): ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 8.6, 2 H), 6.98 (d, J = 8.6, 2 H), 4.91 (s, 1 H), 4.46 (s, 1H), 4.01 (m, 3 H), 3.91 (m, 1 H), 3.72 (m, 1 H), 3.51 m, 1 H), 3.32 (m, 1 H), 2.18 (m, 1 H), 1.78 (m, 3 H), 1.56 (m, 3 H), 1.45 (m, 2 H), 1.13 (m, 3 H), 1.01 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.76, 164.25, 131.55, 130.61, 115.74, 69.21, 66.67, 60.06, 32.25, 24.95, 23.28, 21.96, 20.21, 14.12; MS (ESI) 449 (M^+), 466 (MNH_3^+). Anal. ($C_{18}H_{28}N_2O_7S_2 \cdot 0.5\ H_2O$) C, H, N.

Methyl *N*-[(4-Methoxyphenyl)sulfonyl]-*S*-(2-hydroxyethyl)-D-penicillamine (6a). Following procedure A above (for the preparation of compound **1a**), the title compound was prepared from d-penicillamine methyl ester hydrochloride (19.9 g, 0.1 mol) and 2-bromoethanol (15 g, 0.12 mol, 1.2 equiv). The desired product **6a** was obtained as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.6, 2 H), 6.88 (d, J = 8.6, 2 H), 5.83 (d, J = 11, 1 H), 3.78 (s, 3 H), 3.77 (m, 1 H), 3.63 (br m, 2 H), 3.38 (s, 3 H), 2.75 (br m, 2 H), 2.42 (br s, 1 H), 1.38 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.17, 162.86, 130.71, 129.29, 113.91, 63.57, 61.14, 55.46, 51.99, 46.70, 31.53, 26.31, 26.03.

Methyl 4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethyl-3(*S*)-thiomorpholinecarboxylate (7a). Following procedure A above (for the preparation of compound **2a**) the title compound was prepared. The desired product **7a** was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 8.6, 2 H), 6.92 (d, J = 8.6, 2 H), 4.38 (s, 1 H), 4.01 (m, 1 H), 3.83 (s, 3 H), 3.72 (dt, J_d = 2.9, 12.5, 1 H), 3.39 (s, 3 H), 3.10 (dt, J_d = 3, J_t= 13, 1 H), 2.42 (m, 1 H), 1.59 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.48, 162.73, 130.29, 128.92, 113.85, 62.55, 55.40, 51.13, 40.94, 39.87, 28.21, 27.01, 24.40; MS (ESI) 360 (M^+), 377 (MNH_3^+).

4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethyl-3(*S*)-thiomorpholinecarboxylic Acid (8a). Following procedure A above (for the preparation of compound **3a**) the title compound **8a** was prepared as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.8, 2 H), 6.91 (d, J = 8.8, 2 H), 4.44 (s, 1 H), 3.99 (m, 1 H), 3.81 (s, 3 H), 3.68 (dt, J_d = 3, J_t = 12.5, 1 H), 3.08 (dt, J_d = 3.6, J_t = 12.7, 1 H), 2.40 (m, 1 H), 1.58 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.92, 162.78, 130.41, 129.06, 113.91, 62.75, 55.39, 40.90, 39.76, 28.39, 27.23, 24.31. MS (ESI) 346 (M^+), 363 (MNH_3^+).

***N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-3(*S*)-thiomorpholinecarboxamide (9a).** Following procedure A above (for the preparation of compound **4a**) the title compound **9a** was prepared as a solid which was recrystallized from CH_3CN/H_2O to provide a white powder: ^{1}H NMR (CD_3OD) δ 7.68 (d, J = 8.8, 2 H), 7.03 (d, J = 8.8, 2 H), 4.08 (s, 1 H), 3.88 (m, 1 H), 3.86 (s, 3 H), 3.02 (m, 1 H), 2.44 (m, 1 H), 1.57 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (CD_3OD) δ 167.01,

164.61, 132.01, 130.30, 115.38, 61.01, 56.14, 42.75, 40.64, 29.12, 27.27, 25.54; MS (ESI) 378 (MNH_3^+), 361 (M^+). Anal. ($C_{14}H_{20}N_2O_5S_2$) C, H, N.

***N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-3(*S*)-thiomorpholinecarboxamide 1,1-Dioxide (10a).** The hydroxamic acid **9a** (0.30 g, 0.83 mmol) was dissolved in chloroform (10 mL) to form a suspension. Peracetic acid (0.20 g, 2.5 mmol, 3.0 equiv) was then added and the resulting mixture was stirred overnight at room temperature. The solvent was then removed under reduced pressure. Purification was achieved through crystallization with acetonitrile to form a white powder: ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.6, 2 H), 6.90 (d, J = 8.6, 2 H), 4.60 (m, 1 H), 4.49 (m, 1 H), 3.85 (s, 3 H), 3.21 (m, 1 H), 3.24 (m, 4 H), 1.53 (s, 3H), 1.30 (s, 3 H); MS (ESI) 393.0 (M^+). Anal. ($C_{14}H_{20}N_2O_7S_2$) C, H, N.

***N*-Hydroxy-*N*-methyl-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (12a).** The carboxylic acid **3a** (1.10 g, 3.06 mmol) in dichloromethane (25 mL) was stirred at room temperature and then oxalyl chloride (0.80 g, 6.27 mmol, 2.05 equiv) and DMF (0.22 g, 3.06 mmol) were added. The resulting solution was stirred at room temperature for 30 min. In a separate flask, *N*-methylhydroxylamine hydrochloride (1.02 g, 12.24 mmol, 4 equiv) in THF (8 mL) and water (2 mL) were stirred at 0 °C. Triethylamine (1.85 g, 18.4 mmol, 6 equiv) was added and the resulting solution was stirred at 0 °C for 15 min. The acid chloride solution was next added to the hydroxylamine solution at 0 °C and the resulting mixture was allowed to stir overnight at room temperature. The reaction mixture was acidified with 1 N HCl and then extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated to a solid under reduced pressure. The solid was purified by reverse phase (C_{18}) HPLC chromatography to provide a white powder (0.69 g, 58%): ^{1}H NMR (CD_3OD) δ 7.7842 (d, J = 8.6, 2 H), 7.03 (d, J = 8.6, 2 H), 5.41 (s, 1 H), 4.64 (m, 1 H), 3.83 (s, 3 H), 3.31 (m, 1 H), 3.02 (s, 3 H), 2.82 (m, 1 H), 2.70 (m, 1 H), 2.16 (m, 1 H), 1.79 (m, 1 H), 1.53 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (CD_3OD) δ 170.76, 164.50, 132.44, 130.43, 115.09, 59.93, 56.18, 44.46, 36.11, 33.21, 30.39, 27.35, 26.01; MS (ESI) 389 (M^+). Anal. ($C_{16}H_{24}N_2O_5S_2$) C, H, N.

***N*-Hydroxy-*N*-methyl-4-[(4-phenoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (12h).** Following the procedure for the preparation of **12a**, the carboxylic acid **3h** (0.42 g, 0.98 mmol) was converted to the *N*-methylhydroxamic acid **12h** (0.22 g, 55%) as a colorless solid (purified by reverse phase (C_{18}) HPLC chromatography): ^{1}H NMR (DMSO-d_6) δ 10.23 (s, 1 H), 7.77 (d, J = 8.8, 2 H), 7.49 (t, J = 7.9, 2 H), 7.28 (t, J = 7.3, 1 H), 7.09 (d, J = 8.8, 2 H), 5.28 (s, 1 H), 4.67 (m, 1 H), 3.21 (m, 1 H), 2.94 (s, 3 H), 2.74 (m, 2 H), 2.05 (m, 1 H), 1.83 (m, 1 H), 1.49 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 168.50, 161.26, 155.58, 133.80, 131.10, 129.95, 125.62, 120.69, 118.13, 58.70, 48.22, 43.70, 36.05, 32.45, 30.43, 26.59, 26.03; MS (ESI) 451 (M^+). Anal. $C_{21}H_{26}N_2O_5S_2$ (C, H, N).

***N*-Methoxy-4-[(4-phenoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (13f).** The carboxylic acid **3f** (0.43 g, 1.02 mmol) in dichloromethane (10 mL) was stirred at room temperature and then oxalyl chloride (0.27 g, 2.09 mmol, 2.05 equiv) and DMF (75 mg, 1.02 mmol) were added. The resulting solution was stirred at room temperature for 30 min. In a separate flask, *O*-methylhydroxylamine hydrochloride (0.34 g, 4.08 mmol, 4 equiv) in THF (8 mL) and water (2 mL) were stirred at 0 °C. Triethylamine (0.62 g, 6.12 mmol, 6 equiv) was added and the resulting solution was stirred at 0 °C for 15 min. The acid chloride solution was next added to the hydroxylamine solution at 0 °C and the resulting mixture was allowed to stir overnight at room temperature. The reaction mixture was acidified with 1 N HCl and then extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated to a solid under reduced pressure. The solid was purified by reverse-phase (C_{18}) HPLC chromatography to provide a white powder (0.25 g, 60%): ^{1}H NMR (DMSO-d_6) δ 11.32 (s, 1 H), 7.83 (d, J = 8.8, 2 H), 7.49 (t, J = 7.4, 2 H), 7.27 (t, J = 7.3, 1 H), 7.11 (d, J = 8.8, 2 H), 4.70 (m, 1 H), 4.05 (s, 1 H), 3.40 (m, 4 H), 2.74 (m, 2 H), 2.08 (m, 1 H), 1.83 (m, 1 H), 1.47 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 164.63, 161.14, 155.16, 133.69, 130.78, 129.80, 125.35, 120.40, 117.95, 63.30, 62.60, 47.45, 43.47, 31.88, 29.71, 26.03, 25.94; MS (ESI) 451 (M^+). Anal. ($C_{21}H_{26}N_2O_5S_2$) C, H, N.

6,6-Dimethyl-7-carbomethoxy-tetrahydro-2(3*H*)-azepinone (15). The methyl 2,2-dimethyl-6-oxocyclohexanecarboxylate[23] (**14**) (7.3 g, 39.7 mmol) was dissolved in chloroform (180 mL) and cooled to 0 °C. Methanesulfonic acid (38.1 g, 397 mmol) was added followed by the addition of sodium azide. The reaction mixture was stirred at room temperature for 30 min and then heated to reflux for 5 h. Ice was added to the reaction mixture and stirred for several minutes; this was followed by the addition of ammonium hydroxide until the reaction became basic. The mixture was then extracted with methylene chloride, and the organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to an oil (6.13 g, 68% yield): ^{1}H NMR ($CDCl_3$) δ 6.04 (br s, 1 H), 3.64 (s, 3 H), 2.43 (m, 2 H), 1.71 (m, 2 H), 1.50 (m, 2 H), 0.98 (s, 3 H), 0.96 (s, 3 H); MS (ESI) 200 (M^+).

2-Hydroxymethyl-3,3-dimethyl-hexahydro-1*H*-azepine. The amide **15** (3.75 g, 18.9 mmol) was dissolved in THF (100 mL) under an argon atmosphere at room temperature. Lithium aluminum hydride (1.5 g, 37.7 mmol, 2 equiv) was next added slowly to the reaction mixture. The reaction mixture was heated to reflux for 5 h. The mixture was quenched by the slow, dropwise addition of ethyl acetate until bubbling of the reaction mixture ceased. Then, water (1.5 mL) was added to the solution. A 15% NaOH solution (1.5 mL) was next added followed by water (3.0 mL). The resulting heterogeneous mixture was then filtered, and the remaining organic layer was diluted with water and extracted with ether. The organic layers were dried over sodium sulfate and concentrated under reduced pressure: ^{1}H NMR ($CDCl_3$) δ 4.08 (m, 1 H), 3.83 (m, 1 H), 3.58 (m, 2 H), 3.15 (m, 1 H), 2.66 (m, 1 H), 2.40 (m, 1 H), 1.70 (m, 1 H), 1.47 (m, 1 H), 1.19 (m, 1 H), 0.93 (s, 3 H), 0.80 (s, 3 H); MS (ESI) 158 (M^+).

1-[(4-Methoxyphenyl)sulfonyl]-2-hydroxymethyl-3,3-dimethyl-hexahydro-1*H*-azepine (16). The 2-hydroxymethyl-3,3-dimethyl-hexahydro-1*H*-azepine (2.9 g, 18.9 mmol) was dissolved in a 1:1 mixture of water and *p*-dioxane (100 mL), followed by the addition of 4-methoxyphenylsulfonyl chloride (4.7 g, 22.6 mmol) and triethylamine (7.86 mL, 56.5 mmol). The reaction mixture was stirred overnight. The reaction was quenched and acidified with 1 N HCl to a pH ~ 2. The mixture was then diluted with water and extracted with methylene chloride. The organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The compound was purified by silica gel chromatography using hexane:ethyl acetate (3:2) as the eluent: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.6, 2 H), 6.92 (d, J = 8.6, 2 H), 3.85 (s, 3 H), 3.71 (m, 2 H), 3.60 (m, 2 H), 3.31 (m, 1 H), 3.05 (m, 2 H), 1.85 (m, 2 H), 1.52 (m, 4 H), 0.98 (s, 3 H), 0.91 (s, 3 H); MS (ESI) 328 (M^+), 345 (MNH_3^+).

1-[(4-Methoxyphenyl)sulfonyl]-3,3-dimethyl-hexahydro-1*H*-azepine-2-carboxylic Acid. The alcohol **16** (0.40 g, 1.22 mmol) was dissolved in acetone (50 mL) and freshly prepared 8 N Jones reagent was added until the solution sustained an orange/brown color as opposed to a green color. The reaction mixture was then stirred overnight. 2-Propanol was added to quench the excess Jones reagent and a green solid precipitated out of solution. The solid was filtered through Celite, and the liquid was concentrated under reduced pressure. The residue was then dissolved in chloroform and washed with water several times. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The product was carried forward with no further purification: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.6, 2 H), 6.92 (d, J = 8.6, 2 H),4.23 (br s, 1 H), 3.82 (s, 3 H), 3.71 (m, 2 H), 3.60 (m, 2 H), 3.05 (m, 2 H), 1.60 (m, 2 H), 1.32 (m, 3 H), 1.08 (s, 3 H), 0.90 (s, 3 H); MS (ESI) 342 (M^+), 359 (MNH_3^+).

***N*-Hydroxy-1-[(4-methoxyphenyl)sulfonyl]-3,3-dimethyl-hexahydro-1*H*-azepine-2-carboxamide (17).** The 1-[(4-

methoxyphenyl)sulfonyl]-3,3-dimethyl-hexahydro-1*H*-azepine-2-carboxylic acid (0.37 g, 1.07 mmol) was converted to the desired hydroxamic acid **17** following procedure A above (for the preparation of compound **4a**). The resulting solid was recrystallized from CH_3CN/H_2O to provide the desired product as a white powder: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.6, 2 H), 7.01 (d, J = 8.6, 2 H),4.90 (s, 1 H), 4.03 (s, 1 H), 3.85 (s, 3 H), 3.72 (m, 2 H), 3.55 (m, 1 H), 3.28 (m, 1 H), 2.00 (m, 1 H),1.80 (m, 2 H), 1.60 (m, 2 H), 1.38 (m, 2 H), 1.08 (s, 3 H), 0.98 (s, 3 H); MS (ESI) 357 (M^+). Anal. ($C_{16}H_{24}N_2O_5S$) C, H, N.

7-Carbomethoxy-tetrahydro-2(3*H*)-azepinone (18). Ethyl 2-cyclohexanonecarboxylate (15.0 g, 88.12 mmol) was dissolved in chloroform (200 mL) and cooled to 0 °C. Methanesulfonic acid (84.7 g, 881.2 mmol) was added followed by the addition of sodium azide. The reaction mixture was stirred at room temperature for 30 min and then heated to reflux for 5 h. Ice was added to the reaction mixture and the resulting solution was stirred for several minutes. Ammonium hydroxide was added until the reaction was made basic. The mixture was extracted with methylene chloride, and the organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to an oil: ^{1}H NMR ($CDCl_3$) δ 6.41 (br s, 1 H), 4.20 (m, 1 H), 4.03 (m, 1 H), 2.38 (m, 2 H), 2.19 (m, 1 H), 1.83 (m, 1 H), 1.56 (m, 4H), 1.20 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 175.96, 171.11, 61.87, 55.61, 36.75, 33.49, 29.34, 22.63, 13.83; MS (ESI) 186 (M^+).

2-Hydroxymethyl-hexahydro-1*H*-azepine. The amide **18** (5.0 g, 27.0 mmol) was dissolved in THF (100 mL) under an argon atmosphere at room temperature. Lithium aluminum hydride (2.0 g, 54.0 mmol, 2 equiv) was then cautiously added. The reaction mixture was heated to reflux for 5 h. The mixture was quenched by the slow, dropwise addition of ethyl acetate until bubbling of the reaction mixture ceased. Then, water (2.0 mL) was added to the solution. A 15% NaOH (2.0 mL) was next added followed by water (5.0 mL). The resulting homogeneous solution was filtered, and the remaining organic layer was diluted with water and extracted with ether. The organic layers were dried over sodium sulfate and concentrated under reduced pressure.

1-[(4-Methoxyphenyl)sulfonyl]-2-hydroxymethyl-hexahydro-1*H*-azepine (20). The 2-hydroxymethyl-hexahydro-1*H*-azepine (3.0 g, 23.5 mmol) was dissolved in a 1:1 mixture of water and *p*-dioxane (100 mL) followed by the addition of 4-methoxyphenylsulfonyl chloride (5.8 g, 28.2 mmol) and triethylamine (9.8 mL, 70.5 mmol). The reaction mixture was left to stir overnight. The reaction was quenched and acidified with 1 N HCl to a pH $\sim$ 2. The reaction mixture was then diluted with water and extracted with methylene chloride. The organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The compound was purified by silica gel chromatography using hexane: ethyl acetate (2:1) as the eluent: ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 8.6, 2 H), 6.88 (d, J = 8.6, 2 H),3.91 (m, 1 H), 3.82 (s, 3 H), 3.78 (m, 1 H), 3.46 (m, 2 H), 3.04 (m, 1 H), 2.05 (m, 2 H), 1.64 (br m, 4 H), 1.22 (m, 2 H), 0.86 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 162.45, 133.10, 129.33, 113.90, 66.71, 58.85, 55.36, 42.60, 29.37, 28.14, 26.75, 23.83; MS (ESI) 300 (M^+), 317 (MNH_3^+).

1-[(4-Methoxyphenyl)sulfonyl]-hexahydro-1*H*-azepine-2-carboxylic Acid. The alcohol **20** (1.3 g, 4.35 mmol) was dissolved in acetone (100 mL) at 0 °C and freshly prepared 8 N Jones reagent was added until the solution sustained an orange/brown color as opposed to a green color. The resulting mixture was then stirred overnight. 2-Propanol was added to quench the excess Jones reagent and a green solid precipitated out. The solid was filtered through Celite, and the liquid was concentrated under reduced pressure. The residue was then dissolved in chloroform and washed with water several times. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The product was carried forward with no further purification: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.6, 2 H), 6.91 (d, J = 8.6, 2 H), 4.52 (m, 1H), 3.91 (m, 1 H), 3.82 (s, 3 H), 3.78 (m, 1 H), 3.26 (m, 1 H), 2.25 (m, 1 H), 1.64 (br m, 4 H), 1.22 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 176.95, 162.58, 131.77, 129.19, 113.79, 58.36, 55.37, 44.93, 31.60, 29.54, 29.06, 24.76; MS (ESI) 314 (M^+), 331 (MNH_3^+).

***N*-Hydroxy-1-[(4-methoxyphenyl)sulfonyl]-hexahydro-1*H*-azepine-2-carboxamide (21).** The 1-[(4-methoxyphenyl)-sulfonyl]-hexahydro-1*H*-azepine-2-carboxylic acid (1.11 g, 3.56 mmol) was converted to the desired hydroxamic acid **21** following procedure A above (for the preparation of compound **4a**). The resulting solid was recrystallized from CH_3CN/H_2O to provide a white powder: ^{1}H NMR ($CDCl_3$) δ 10.89 (s, 1 H), 7.74 (d, J = 8.6, 2 H), 6.90 (d, J = 8.6, 2 H), 4.34 (m, 1H), 3.84 (s, 3 H), 3.69 (m, 1 H), 3.32 (m, 1 H), 2.18 (m, 2 H), 1.71 (br m, 4 H), 1.30 (m, 2 H), 1.15 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 185.85, 180.89, 170.06, 129.34, 114.24, 55.45, 45.33, 30.13, 29.01, 28.35, 24.22; MS (ESI) 429 (M^+); HRMS calcd 329.1171, found 329.1171.

Methyl *N*-[(4-Methoxyphenyl)sulfonyl]-*S*-(2-hydroxypentyl)-D-penicillamine (25). Following procedure A above, D-penicillamine (5.0 g, 33.5 mmol) and 1-chloropentanol (4.92 g, 40.2 mmol, 1.2 equiv) were converted to the title compound which was obtained as a colorless oil. Purification of the methyl ester was accomplished by chromatography on silica gel using 6/4 hexane/EtOAc as the eluent. The desired product (2.20 g, 15%) was obtained as a clear, colorless oil: ^{1}H NMR (CD_3OD) δ 7.74 (d, J = 8.2, 2 H), 6.92 (d, J = 8.2, 2 H), 5.42 (d, J = 8.2, 1 H), 3.81 (s, 3 H), 3.76 (d, J = 8.1, 1 H), 3.61 (t, J = 6.1, 2 H), 3.41 (s, 3 H), 2.40 (m, 2 H), 1.60−1.38 (m, 6 H), 1.38 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (CD_3OD) δ 186.05, 170.13, 162.85, 130.64, 129.33, 113.89, 62.84, 62.39, 55.46, 51.89, 46.45, 32.00, 28.70, 27.78, 25.80, 25.62, 24.96; MS (ESI) 420 (M^+), 437 (MNH_3^+).

Methyl *N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-octahydro-1,4-thiazonine-3(*S*)-carboxylate (27). The methyl ester **25** (2.1 g, 5.0 mmol) was converted to the title compound as a colorless oil (0.50 g, 25%) following procedure A (for the preparation of compound **2a**): ^{1}H NMR (CD_3OD) δ 7.74 (d, J = 8.2, 2 H), 6.94 (d, J = 8.2, 2 H), 4.56 (s, 1 H), 3.83 (m, 1 H), 3.81 (s, 3 H), 3.30 (s, 3 H), 2.84 (m, 2 H), 2.56 (m, 1 H), 2.30 (m, 1 H), 2.03 (m, 1 H), 1.63 (m, 2 H), 1.53 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (CD_3OD) δ 167.74, 162.83, 130.48, 128.26, 113.30, 68.32, 55.41, 50.88, 48.21, 45.85, 31.42, 30.59, 29.44, 29.11, 27.81, 24.53, 22.41, 20.81, 13.90; MS (ESI) 402 (M^+), 419 (MNH_3^+).

4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethyl-octahydro-1,4-thiazonine-3(*S*)-carboxylic Acid. The methyl ester **27** (0.44 g, 1.10 mmol) was converted to the desired carboxylic acid following procedure A (for the preparation of compound **3a**). The resulting oil was purified by column chromatography using 1/1 hexane/EtOAc as the eluent to provide the desired product as a light yellow oil (0.395 g, 93%): MS (ESI) 388 (M^+), 405 (MNH_3^+).

***N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-octahydro-1,4-thiazonine-3(*S*)-carboxamide (22).** The 4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-octahydro-1,4-thiazonine-3(*S*)-carboxylic acid (392 mg, 1.01 mmol) was converted to the desired hydroxamic acid **22** following procedure A (for the preparation of compound **4a**). The resulting solid was recrystallized from CH_3CN to provide a white powder (0.25 g, 62%): ^{1}H NMR (CD_3OD) δ 7.72 (d, J = 8.2, 2 H), 6.98 (d, J = 8.2, 2 H), 4.62 (m, 1 H), 4.05 (s, 1 H), 3.81 (s, 3 H), 2.84 (m, 2 H), 2.58 (m, 1 H), 2.15 (m, 1 H), 2.02 (m, 1 H), 1.63 (m, 4 H), 1.45 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (CD_3OD) δ 166.21, 164.76, 131.44, 129.91, 115.40, 65.75, 55.54, 47.64, 32.79, 30.87, 30.77, 30.45, 29.19, 26.23; MS (ESI) 420 (MNH_3^+), 403 (M^+). Anal. ($C_{17}H_{26}N_2O_5S_2$) C, H, N.

***N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-octahydro-7-oxa-1,4-thiazonine-3(*S*)-carboxamide (23).** Following the procedure described above for the preparation of **22**, the 4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-octahydro-7-oxa-1,4-thiazonine-3(*S*)-carboxylic acid (1.95 g, 5.0 mmol) was converted to the desired hydroxamic acid **23** (0.25 g, 62%) as a white powder (recrystallized from CH_3CN): ^{1}H NMR (DMSO-d_6) δ 10.61 (s, 1 H), 8.85 (s, 1 H), 7.75 (d, J = 8.9, 2 H), 7.07 (d, J = 8.9, 2 H), 5.10 (m, 1 H), 4.05 (m, 2 H), 4.01 (s, 1 H), 3.85 (s, 3 H), 3.40 (m, 3 H), 2.83 (m, 2 H), 2.55 (m, 1 H), 1.34 (s, 3 H), 1.31 (s, 3 H); MS (ESI) 405 (MH^+). Anal. ($C_{16}H_{24}N_2O_6S_2$) C, H, N.

***N*-Hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-octahydro-7-oxa-1,4-thiazonine-3(*S*)-carboxamide 1,1-Dioxide (24).** Following the procedure described above for the preparation of **5a**, the *N*-hydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-octahydro-7-oxa-1,4-thiazonine-3(*S*)-carboxamide (**23**) (0.70 g, 1.73 mmol) was converted to the desired hydroxamic acid **24** (0.60 g, 79%) as a white powder (triturated from CH_3CN/H_2O): ^{1}H NMR (DMSO-d_6) δ 11.11 (s, 1 H) 8.95 (s, 1 H), 7.78 (d, J = 9.0, 2 H), 7.07 (d, J = 9.0, 2 H), 4.74 (s, 1 H), 4.23 (m, 2 H), 3.98 (m, 2 H), 3.86 (s, 3 H), 3.76 (m, 2 H), 3.40 (m, 1 H), 3.12 (m, 1 H), 1.73 (s, 3 H), 1.33 (s, 3 H); MS (ESI) 435 (MH^-). Anal. ($C_{16}H_{24}N_2O_8S_2 \cdot 0.25H_2O$) C, H, N.

Methyl *N*-[(4-Methoxyphenyl)sulfonyl]-*S*-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-D-penicillamine (29). D-Penicillamine (9.56 g, 64.1 mmol) in 2 N NaOH (41.7 mL, 83.3 mmol, 1.3 equiv) was stirred at 0 °C under an argon atmosphere. A solution of (*S*)-4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane[25] (15.0 g, 76.9 mol, 1.2 equiv) in ethanol (30 mL) was slowly added dropwise to the reaction mixture at 0 °C. The resulting solution was stirred overnight at room temperature and then the mixture was acidified to pH ~ 6 with 1 N HCl. The solvent was removed under reduced pressure to leave a thick oil. The penicillamine adduct was then dissolved in dioxane (75 mL) and water (75 mL) and stirred at room temperature. Triethylamine (19.5 g, 192.3 mmol, 3 equiv) was then added to the reaction mixture followed by 4-methoxyphenylsulfonyl chloride (15.9 g, 76.9 mmol). The resulting homogeneous solution was stirred at room temperature for 18 h and then acidified to pH ~ 2 with 1 N HCl. The solution was poured into water and extracted with methylene chloride. The organic extracts were dried ($MgSO_4$) and concentrated to an oil under reduced pressure. The resulting oil was diluted in methanol (30 mL) and enough diazomethane in diethyl ether was added to form a yellow solution. The mixture was concentrated under reduced pressure to leave a colorless oil. Purification of the resulting methyl ester was accomplished by chromatography on silica gel using 8/2 hexane/EtOAc as the eluent. The desired product (11.2 g, 43%) was obtained as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.6, 2 H), 6.91 (d, J = 8.6, 2 H), 5.44 (d, J = 11, 1 H), 4.04 (m, 3 H), 3.82 (s, 2 H), 3.78 (d, J = 11, 1 H), 3.63 (m, 2 H), 3.40 (s, 3 H), 2.59 (m, 2 H), 2.44 (m, 2 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.00, 162.88, 130.61, 129.32, 113.89, 109.39, 74.64, 68.51, 62.83, 60.16, 55.44, 51.93, 46.68, 31.44, 26.62, 25.84, 25.43, 25.25; MS (ESI) 448 (M^+), 465 (MNH_3^+).

Methyl 2(*S*)-*N*-[(4-Methoxyphenyl)sulfonyl]-*S*-(2,3-dihydroxypropyl)-D-penicillamine (30). The acetonide **29** (11.1 g, 24.8 mmol) in THF (50 mL) was stirred at room temperature and the 1 N HCl was added The resulting mixture was stirred overnight at room temperature until all of the starting material was consumed. The reaction mixture was concentrated to remove the THF and then the aqueous layer was extracted with methylene chloride. The organic extracts were dried (Na_2SO_4) and concentrated to an oil under reduced pressure. No further purification was performed. The product (10.0 g, 99%) was obtained as a colorless oil.

Methyl *N*-[(4-Methoxyphenyl)sulfonyl]-*S*-(2(*S*)-hydroxy-3-*tert*-butyldimethylsiloxypropyl)-D-penicillamine. The diol **30** (10.0 g, 24.5 mmol) in methylene chloride (150 mL) was stirred at room temperature and then triethylamine (2.73 g, 27 mmol, 1.1 equiv) and (dimethylamino)pyridine (100 mg, 0.04 equiv) were added. The *tert*-butyldimethylsilyl chloride (3.7 g, 24.5 mmol) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into dilute sodium bicarbonate solution and extracted with methylene chloride. The organic extracts were dried (Na_2SO_4) and then concentrated to an oil under reduced pressure. Purification of the oil was accomplished by chromatography on silica gel using 7/3 hexane/EtOAc as the eluent. The product (10.5 g, 82%) was obtained as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 8.6, 2 H), 6.85 (d, J = 8.6, 2 H), 5.62 (d, J = 11, 1 H), 3.81 (s, 3 H), 3.60 (m, 3 H), 3.37 (s, 3 H), 2.59 (m, 2 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 0.84 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.12, 162.83, 130.72, 129.32, 113.87, 70.55, 65.38, 63.22, 55.44, 51.94, 46.67, 31.31, 26.21, 25.72, 18.04.

Methyl *N*-[(4-Methoxyphenyl)sulfonyl]-*S*-(2(*S*)-methoxymethoxy-3-*tert*-butyldimethylsiloxypropyl)-D-penicillamine (31). Sodium iodide (12.0 g, 80 mmol, 4 equiv) was stirred in dimethoxyethane (120 mL) at room temperature and then chloromethyl methyl ether (8.2 g, 102 mmol, 5.1 equiv) was added. A brown suspension formed which became hot to touch. The resulting mixture was stirred for 10 min and the methyl *N*-[(4-methoxyphenyl)sulfonyl]-*S*-(2(*S*)-hydroxy-3-*tert*-butyldimethylsiloxypropyl)-D-penicillamine (10.5 g, 20 mmol) and diisopropylethylamine (14.3 g, 110 mmol, 5.5 equiv) in dimethoxyethane (30 mL) were added. The mixture was stirred at room temperature for 1 h and then heated to reflux for 4 h. The reaction mixture was poured into saturated sodium bicarbonate solution and then extracted with methylene chloride. The organic extracts were dried (Na_2SO_4) and then concentrated to an oil under reduced pressure. The oil was purified by chromatography on silica gel using 8/2 hexane/EtOAc as the eluent. The product (8.1 g, 71%) was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.5, 2 H), 6.89 (d, J = 8.5, 2 H), 5.49 (d, J = 11, 1 H), 4.61 (m, 3 H), 3.81 (s, 3 H), 3.60 (m, 3 H), 3.40 (s, 6 H), 2.59 (br m, 2 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 0.83 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.01, 162.81, 130.81, 129.31, 113.84, 96.00, 77.50, 64.27, 63.08, 55.42, 51.82, 46.66, 29.85, 26.26, 25.65 18.04.

Methyl *N*-[(4-Methoxyphenyl)sulfonyl]-*S*-(2(*S*)-methoxymethoxy-3-hydroxypropyl)-D-penicillamine (32). The silyl ether **31** (3.16 g, 5.58 mmol) in THF (25 mL) was cooled to 0 °C and then tetrabutylammonium fluoride (1.0 M in THF, 14 mL, 2.5 equiv) was added. The resulting mixture was stirred at 0 °C for 30 min and warmed to room temperature. The reaction mixture was stirred for an additional 3 h. The reaction mixture was poured into saturated sodium bicarbonate solution and then extracted with methylene chloride. The organic extracts were dried (Na_2SO_4) and then concentrated to an oil under reduced pressure. The oil was purified by chromatography on silica gel using 1/1 hexane/EtOAc as the eluent. The product (1.96 g, 78%) was obtained as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.6, 2 H), 6.83 (d, J = 8.6, 2 H), 5.64 (d, J = 11, 1 H), 4.61 (m, 2 H), 3.82 (s, 3 H), 3.58 (m, 3 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 2.81 (m, 1 H), 2.61 (br m, 2 H), 1.31 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.97, 162.83, 130.68, 129.28, 113.87, 96.27, 79.00, 63.77, 63.07, 55.57, 55.45, 51.92, 46.62, 29.28, 25.96, 25.65.

Methyl 6(*S*)-Methoxymethyl-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylate (33). The methyl ester **32** (1.9 g, 4.3 mmol) in THF (15 mL) was stirred at room temperature followed by the addition of triphenylphosphine (1.35 g, 5.16 mmol, 1.2 equiv) and diethyl azodicarboxylate (0.82 g, 4.73 mmol, 1.1 equiv). The resulting solution was stirred at room temperature for 2 h. The solvent was removed and then the thick yellow oil was diluted with methylene chloride and silica gel (20 g) was added. The solvent was removed to leave a white powder. This powder was placed upon a chromatography column and eluted with 8/2 hexane/EtOAc. The desired product (1.60 g, 86%) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 8.8, 2 H), 6.95 (d, J = 8.8, 2 H), 4.74 (AB, J = 6.7, 42.3, 2 H), 4.40 (m, 2 H), 4.00 (m, 2 H), 3.86 (s, 3 H), 3.42 (s, 3 H), 3.41 (s, 3 H), 2.80 (m, 2 H), 1.55 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.07, 163.19, 131.19, 130.12, 114.09, 95.13, 77.71, 67.29, 55.85, 51.69, 46.91, 46.73, 31.21, 29.43, 26.54; MS (ESI) 434 (M^+), 451 (MNH_3^+).

6(*S*)-Methoxymethyl-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylic Acid. The methyl ester **33** (2.2 g, 5.07 mmol) in pyridine (40 mL) was stirred at room temperature under an argon atmosphere. Lithium iodide (8.15 g, 61.9 mmol, 12 equiv) was added and the resulting solution was heated to reflux for 3 h. The reaction mixture was cooled to room temperature and then the solution was acidified with 1 N HCl. The mixture was extracted with methylene chloride and then the organic

extracts were dried (Na_2SO_4) and concentrated to an oil under reduced pressure. The oil was purified by column chromatography using 1/1 hexane/EtOAc as the eluent to provide the desired product (1.98 g, 93%) as a light yellow oil: ^{13}C NMR ($CDCl_3$) δ 176.59, 163.66, 132.54, 132.22, 115.22, 95.30, 79.35, 56.47, 56.27, 46.22, 31.09, 29.33, 27.41; MS (ESI) 420 (M^+), 437 (MNH_3^+), 442 (MNa^+).

***N*-Hydroxy-6(*S*)-methoxymethyl-4-[(4-methoxyphenyl)-sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (34).** The 6(*S*)-methoxymethyl-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylic acid (2.35 g, 5.6 mmol) was converted to the desired hydroxamic acid **34** following procedure A above (for the preparation of compound **4a**). The solid was purified by reverse-phase HPLC using 60/40 water/acetonitrile as the eluent to provide a white powder (1.35 g, 56%): ^{1}H NMR (DMSO-d_6) δ 10.57 (s, 1 H), 8.88 (br s, 1 H). 7.79 (d, J = 9.2, 2 H), 7.09 (d, J = 9.2, 2 H), 4.95 (dd, J = 3.7, 16.1, 1 H), 4.62 (dd, J = 7.0, 34.6, 2 H), 3.99 (s, 1 H), 3.84 (s, 3 H), 3.67 (m, 1 H), 3.34 (m, 1 H), 3.28 (s, 3 H), 2.78 (m, 1 H), 2.57 (m, 1 H), 1.26 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (CD_3OD) δ 169.97, 164.76, 132.54, 131.08, 115.24, 96.09, 79.81, 64.68, 47.51, 47.30, 31.37, 29.90, 26.60; MS (ESI) 373 (M^+). Anal. ($C_{17}H_{26}N_2O_7S_2$) C, H, N.

***N*-6-Dihydroxy-4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide 1,1 Dioxide (35).** The hydroxamic acid **34** (1.30 g, 2.99 mmol) was dissolved in chloroform (50 mL) and the mixture was stirred at room temperature. A 32% solution of peracetic acid (3.03 mL, 11.97 mmol, 4.0 equiv) was added and the resulting mixture was stirred at room temperature. The solvent and remaining peracetic acid was removed under reduced pressure to leave the desired product as a white solid. The solid was recrystallized from acetonitrile to provide the product (0.76 g, 60%) as a white crystalline solid: ^{1}H NMR (CD_3OD) δ 7.82 (d, J = 9.2, 2 H), 7.09 (d, J = 9.2, 2 H), 4.44 (m, 2 H), 4.31 (m, 1 H), 3.89 (s, 3 H), 3.77 (m, 1 H0, 3.52 (m, 2 H), 1.61 (s, 3 H), 1.46 (s, 3 H); ^{13}C NMR (CD_3OD) δ 163.57, 129.56, 129.16, 113.94, 65.35, 63.85, 60.50, 54.71, 54.17, 49.79, 22.51, 17.98; MS (ESI) 423 (M^+). Anal. ($C_{15}H_{22}N_2O_8S_2$) C, H, N.

Methyl *N*-[(4-Methoxyphenyl)sulfonyl]-*S*-(3-hydroxy-3(*R*)-phenylpropyl)-D-penicillamine. Following procedure A described above, (*R*)-3-chloro-1-phenyl-1-propanol (4.27 g, 25.0 mmol, 1.0 equiv) and D-penicillamine methyl ester hydrochloride (5.0 g, 25.1 mmol) in 1,8-diazabicyclo[5.4.0]-undec-7-ene (7.64 g, 50.2 mmol, 2 equiv) were converted to the desired product as a colorless oil (11.6 g, 99%) under reduced pressure. No further purification was performed: ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 9.0, 2 H), 7.32 (m, 5 H), 6.94 (d, J = 9.0, 2 H), 5.73 (d, J = 8.9, 1 H), 4.79 (dd, J = 4.6, 8.6, 1 H), 3.84 (s, 3 H), 3.80 (d, J = 9.9, 1 H), 3.37 (s, 3 H), 3.23 (br s, 1 H), 2.58 (dd, J = 6.9, 7.7, 2 H), 1.98 (m, 1 H), 1.72 (m, 2 H), 1.35 (s, 3 H), 1.32 (s, 3 H); MS (ESI) 468 (M^+).

Methyl 4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethyl-5(*S*)-phenyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylate. Following procedure A, the methyl *N*-[(4-methoxyphenyl)sulfonyl]-*S*-(3-hydroxy-3(*R*)-phenylpropyl)-D-penicillamine (11.7 g, 25.1 mmol) was converted to the desired product as a thick yellow oil which was subsequently diluted with methylene chloride and silica gel (50 g) was added. The solvent was removed to leave a white powder. This powder was placed upon a chromatography column and eluted with 4/1 hexane/EtOAc. The desired product (3.7 g, 33%) was obtained as a colorless oil. The major product from the reaction resulted from dehydration of the benzyl alcohol to form the undesired styrene derivative: ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 2 H), 6.97 (m, 5 H), 6.48 (d, J = 9.0, 2 H), 5.64 (br m, 1 H), 5.01 (br m, 1 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.00 (m, 1 H), 2.82 (br m, 1 H), 2.58 (br m, 1 H), 2.11 (m, 1 H), 1.70 (m, 6 H); MS (ESI) 450 (M^+).

4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethyl-5(*S*)-phenyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylic Acid. The methyl 4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-5(*S*)-phenyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylate (1.5 g, 3.33 mmol) in pyridine (50 mL) was stirred at room temperature under an argon atmosphere. Lithium iodide (5.35 g, 40 mmol, 12 equiv) was added and the resulting solution was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and then the solution was acidified with 1 N HCl. The mixture was extracted with methylene chloride and then the organic extracts were dried ($MgSO_4$) and concentrated to an oil under reduced pressure. The product was a colorless oil (1.40 g, 95%), which required no further purification: MS (ESI) 436 (M^+).

***N*-Hydroxy-4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethyl-5(*S*)-phenyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (36a).** The 4-[(4-methoxyphenyl)sulfonyl]-2,2-dimethyl-5(*S*)-phenyl-hexahydro-1,4-thiazepine-3(*S*)-carboxylic acid (0.28 g, 0.64 mmol) was converted to the desired hydroxamic acid **36a** following procedure A above (for the preparation of compound **4a**). The resulting solid was triturated from toluene to provide the desired product (0.25 g, 86%) as a white powder: ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1 H), 9.17 (s, 1 H), 7.00 (m, 7 H), 6.60 (d, J = 7.7, 2 H), 5.02 (m, 2 H), 3.73 (s, 3 H), 3.69 (m, 1 H), 2.91 (m, 1 H), 2.63 (m, 1 H), 2.02 (m, 1 H), 1.59 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 164.46, 161.67, 142.67, 133.89, 128.60, 128.15, 127.77, 126.57, 113.56, 69.47, 66.93, 55.88, 46.74, 28.83, 27.46; MS (ESI) 451 (M^+), 468 (MNH_3^+). Anal. ($C_{21}H_{26}N_2O_5S_2$) C, H, N.

***N*-Hydroxy-4-[(4-Methoxyphenyl)sulfonyl]-2,2-dimethyl-5(*S*)-phenyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (36b).** Following the procedure described above for the preparation of **36a** with (*S*)-3-chloro-1-phenyl-1-propanol, the carboxylic acid **39b** (1.0 g, 2.30 mmol) was converted to 0.80 g (79%) of the hydroxamic acid **36b** as a white powder (recrystallized from acetonitrile/water): ^{1}H NMR (DMSO-d_6) δ 11.07 (s, 1 H), 9.10 (s, 1 H), 7.10−6.85 (m, 7 H), 6.58 (d, J = 7.7, 2 H), 6.67 (m, 1 H), 4.42 (s, 1 H), 3.73 (s, 3 H), 2.92 (m, 1 H), 2.86 (m, 1 H), 2.02 (m, 1 H), 1.59 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 173.16, 161.75, 146.95, 139.22, 136.73, 134.52, 130.03, 128.62, 127.78, 127.55, 125.10, 113.29, 67.96, 57.68, 55.62, 47.33, 35.08, 30.36, 26.55, 26.08; MS (ESI) 451 (M^+). Anal. ($C_{21}H_{26}N_2O_5S_2$) C, H, N.

***N*-Hydroxy-4-[(4-Methoxyphenyl)sulfonyl]-3-methyl-hexahydro-1,4-thiazepine-3(*S*)-carboxamide (45).** The title compound was prepared from 2-methyl-D-cysteine[40] following procedure A to provide **45** as a white solid: ^{1}H NMR (CD_3OD) δ 7.88 (d, J = 8.4, 2 H), 7.06 (d, J = 8.4, 2 H), 3.82 (s, 3 H), 3.67 (m, 1 H), 3.57 (m, 2 H), 2.98 (m, 3 H), 2.52 (m, 2 H), 1.59 (s, 3 H); ^{13}C NMR (CD_3OD) δ 173.14, 164.67, 133.82, 131.31, 115.23, 68.47, 56.24, 46.97, 45.47, 34.83, 33.30, 23.27. Anal. ($C_{14}H_{20}N_2O_5S_2 \cdot H_2O$) C, H, N.

Compounds **37**−**44** were prepared in two steps from the corresponding amino acid and 4-methoxyphenylsulfonyl chloride.[17] The carboxylic acid was converted to the desired hydroxamic acid following procedure A for the preparation of **4a**.

Expression and Purification of Human Recombinant Truncated MMP-1. Briefly, DNA sequence coding for Val82-Pro249 of proMMP-1 was amplified by polymerase chain reaction from a commercially available plasmid, p35-1 (ATCC, Rockville, MD; Templeton et al. *Cancer Res.* **1990**, *50*, 5431−5437) encoding human interstitial MMP-1. The PCR fragment was ligated into the expression vector, pET-11a (Novagen, Madison, WI) and expressed in *E. coli* BL21(DE3) cells. The protein was solubilized from inclusion bodies in 6 M urea, 0.15 M NaCl (pH 7.5), refolded in 50 mM Tris-HCl (pH 7.5), 10 mM $CaCl_2$, 0.1 mM zinc acetate, and then purified to homogeneity over a hydroxamic acid inhibitor affinity column as previously described (Moore and Spilburg *Biochemistry* **1986**, *25*, 5189−5195). N-Terminal sequence analysis confirmed the presence of three N-terminal sequences of Val-Leu-Thr-Glu-Gly-Asn, Met-Val-Leu-Thr-Glu-Gly-Asn, and Leu-Thr-Glu-Gly-Asn (minor).

Expression and Purification of Human Recombinant ProMMP-2. A partial cDNA clone for MMP-2 known as K-121 (Tryggvason *J. Biol. Chem.* **1990**, *265*, 11077−11082), was obtained from ATCC and subcloned into the pBlueScript SK$^-$ (pBS) plasmid. Sanger dideoxy sequencing revealed that the

first 134 bp of the coding sequence were missing from the 5′ end of K-121. To restore the missing sequence, two overlapping 90+-mer oligonucleotides were designed and synthesized. These, along with a 3′ antisense oligonucleotide, were used as primers to the K-121 template in a series of polymerase chain reaction (PCR) experiments to synthesize a full-length MMP-2 cDNA. The PCR product was then subcloned into pBS. To express MMP-2 in the mammalian CHO D^- cell system, it was first subcloned into the mammalian expression vector pJT1 (J. Ting, CRD), which contains the DHFR gene. Recombinant MMP-2/pJT1 was Polybrene transfected into CHO D^- cells. Clonal cell populations were isolated and screened for production of MMP-2 mRNA using specific oligonucleotide primers and reverse transcription PCR. Ten clones producing the highest levels of MMP-2 mRNA were selected, and the DHFR/MMP-2 construct was amplified by gradually increasing media methotrexate (MTX, a DHFR inhibitor) concentration. Clonal selection was further narrowed after assessing MMP bioactivity in an MMP fluorescence assay (M. Anastasio, CRD) and on zymogram gels. Those clones showing activity were tested for MMP-2 protein production by sequential Edman degradation protein sequencing (F. Wang, P&GP Cell & Molecular Biology Core) and Western blot. Based on all results, one clone was expanded for growth in roller bottles. Approximately 9 L of serum-free conditioned media with an MMP-2 concentration of ~35 mG/L were generated. ProMMP-2 was purified from conditioned media as previously described (Crabbe et al. *Eur. J. Biochem*. **1993**, *218*, 431−438) with the following modifications. Conditioned serum-free media was reduced in volume with an Amicon S1Y30 spiral-wound cartridge prior to chromatography on a gelatin-Sepharose 4B column equilibrated in 25 mM Tris/HCl, 30 mM NaCl, 10 mM $CaCl_2$ (pH 7.5) (TNC buffer). The column was washed with equilibration buffer before elution of the bound protein by TNC buffer containing 1 M NaCl followed by 1 M NaCl and 10% (by vol) dimethyl sulfoxide (DMSO) in TNC buffer. ProMMP-2 fractions were concentrated in an Amicon ultrafiltration cell with a YM30 membrane and diafiltered against 25 mM MES/NaOH, 30 mM NaCl, 10 mM $CaCl_2$ (pH 6.0) (MNC buffer). The concentrate was then chromatographed over a second gelatin-Sepharose 4B column equilibrated in MNC buffer, washed with equilibration buffer to remove nonbinding proteins, and eluted with MNC buffer containing 0.3 M NaCl and 10% (by vol) DMSO. Elution fractions containing progelatinase A were pooled, diluted, and loaded onto an S−Sepharose Fast Flow column equilibrated in MNC buffer and eluted with MNC buffer containing 0.3 M NaCl. The concentrated fractions of purified proMMP-2 were combined and stored in MNC buffer containing 0.3 M NaCl at −70 °C. N-Terminal sequence, amino acid, and mass spectrophotometric analyses confirmed the identity of the purified protein with the expected sequence for progelatinase A.

Expression and Purification of Human Recombinant Truncated MMP-3. Briefly, DNA sequence coding for Ala1-Thr255 of proMMP-3 was amplified by polymerase chain reaction from a recombinant plasmid encoding human synovial preproMMP-3 kindly provided by Dr. Hideaki Nagase (University of Kansas Medical Center, Kansas City, KS) and Dr. Markku Kurkinen (Department of Medicine, UMDNJ-Robert Wood Johnson Medical School). After DNA sequence verification, this DNA fragment was ligated into the expression vector pET-3d (Novagen, Madison, WI) and expressed in *E. coli* BL21 (DE3) cells as previously described (Marcy et al. *Biochemistry* **1991**, *30*, 6476−6483). ProMMP-3 was solubilized form inclusion bodies in 8 M guanidine-HCl, refolded in 100 mM Tris-HCl (pH 7.5), 10 mM $CaCl_2$, 0.5 mM zinc acetate, and activated overnight at 37 °C with 1.5 mM *p*-aminophenylmercuric acetate. Active, truncated MMP-3 was purified to homogeneity over a hydroxamic acid inhibitor affinity column as described (Moore and Spilburg *Biochemistry* **1986**, *25*, 5189−5195). N-Terminal sequence analysis confirmed the sequence to be consistent with the catalytic domain, Phe83-Thr255, of proMMP-3.

Collagenase (MMP-1) Inhibition Assay. ProMMP-1 was activated prior to assay by treatment with trypsin. MMP-1 activity was monitored using a fluorescence assay previously described.[26] In a Dynatech MicroFLUOR plate, 10 nM activated collagenase was incubated with 8 μM Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 in 50 mM Tris-HCl, 10 mM $CaCl_2$, 0.15 M NaCl, 0.05% Brij for 20−30 min at 37 °C in the presence of varying concentrations of inhibitor. The reaction was then quenched with 50 mM EDTA and the fluorescence increase monitored on a Perkin-Elmer LS50B spectrofluorimeter (λ_{ex} 328 nm, λ_{em} 393 nm). Activity was measured as a percentage of control activity in the absence of inhibitor. Inhibitor concentrations were run in triplicate, and IC_{50} determinations were calculated from a 4-parameter logistic fit of the data within a single experiment.

Stromelysin (MMP-3) Inhibition Assay. ProMMP-3 was activated prior to assay by treatment with *p*-aminophenylmercuric acetate or trypsin. MMP-3 activity was measured by following the degradation of ^{3}H-reduced, carboxymethylated transferrin.[27] In a Multiscreen DP filtration plate (Millipore), 50 ng of activated MMP-3, 30 μg of [^{3}H]transferrin, and varying concentrations of inhibitor were incubated in a buffer of 50 mM Tris-HCl, 10 mM $CaCl_2$, 0.15 M NaCl, 0.05% Brij (pH 7.5) at 37 °C for 3 h. The reaction was quenched by addition of 4.4% TCA, and TCA-soluble fragments were counted for radioactivity. Activity was measured as a percentage of control activity in the absence of inhibitor. Inhibitor concentrations were run in triplicate, and IC_{50} determinations were calculated from a 4-parameter logistic fit of the data within a single experiment.

Gelatinase A (MMP-2), Matrilysin (MMP-7), Neutrophil Collagenase (MMP-8), Gelatinase B (MMP-9), and Collagenase-3 (MMP-13) Inhibition Assay. Inhibition of all enzymes was measured according to the representative procedure described below for MMP-2. ProMMP-2 was activated prior to assay by treatment with 1 mM *p*-aminophenylmercuric acetate for 45 min at 37 °C. ProMMP-9 was activated with MMP-3 (1:20 MMP-3:MMP-9) and stored at −80 °C until use. MMP-7, MMP-8, and MMP-13 were all supplied as active enzymes and stored frozen until use. MMP activity was monitored using a fluorescence assay previously described,[26] modified for a microtiter plate format. In a Dynatech MicroFLUOR plate, active enzyme was incubated with 8 μM Mca-Pro-Leu-Dpa-Ala-Arg-NH_2 in 50 mM Tris-HCl (pH 7.5), 10 mM $CaCl_2$, 0.15 M NaCl, 0.05% Brij for 20−30 min at 37 °C in the presence of varying concentrations of inhibitor. The reaction was then quenched with 50 mM EDTA, and the relative fluorescence was monitored on a Perkin-Elmer LS50B spectrofluorimeter (λ_{ex} 328 nm, λ_{em} 393 nm) fitted with a microplate reader attachment. Activity was measured as a percentage of control activity in the absence of inhibitor. Inhibitor concentrations were run in triplicate, and IC_{50} determinations were calculated from a 4-parameter logistic fit of the data within a single experiment.

MT1-MMP (MMP-14) Inhibition Assay. MT1-MMP was purified according to the methods reported by Ohuchi et al.[28] The inhibitory activity of the test compound to MT1-MMP was determined by using the synthetic protein substrate, the coumarinyl peptide derivative Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2. A mixture of MT-MMP1 (6 nM) and substrate (4 μM) in a total volume of 200 μL of 50 mM Tris-HCl (pH 7.5), 10 mM $CaCl_2$, 0.15 M NaCl, 0.05% Brij was incubated for 20−30 min at 37 °C in the presence of varying concentrations of inhibitor. The reaction was then quenched with 50 mM EDTA, and the relative fluorescence was monitored on a Perkin-Elmer LS50B spectrofluorimeter (λ_{ex} 328 nm, λ_{em} 393 nm) fitted with a microplate reader attachment. Activity was measured as a percentage of control activity in the absence of inhibitor. Inhibitor concentrations were run in triplicate, and IC_{50} determinations were calculated from a 4-parameter logistic fit of the data within a single experiment.

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