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DISCOVERY OF A NOVEL SERIES OF SELECTIVE MMP INHIBITORS: IDENTIFICATION OF THE γ-SULFONE-THIOLS

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Abstract: We have discovered a new series of potent MMP Inhibitors that are selective for MMP-13 over MMP-1 incorporating a γ-sulfone thiol.

Keywords: Enzyme inhibitors, antitumour compds

Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that degrade the major components of the extracelluar matrix. These enzymes can be divided into subfamilies based on the matrix components they degrade. The cleavage of type II collagen, the major constituent of cartilage, is uniquely mediated by collagenases; MMP-1, MMP-8, and MMP-13. Current osteoarthritis therapies treat the associated pain and inflammation, and are mainly pallative. By contrast, MMP inhibitors are disease modifying agents with the potential to prevent the degradation and loss of cartilage. Broad spectrum MMP inhibitors have shown efficacy in two animal models of osteoarthritis; the spontaneous guinea pig and the rabbit partial meniscectomy models thus supporting their potential role in modifying disease progression.[1,2]

MMP inhibitors have been the subject of several recent reviews.[3–5] Most synthetic inhibitors of the various MMP's rely on a functional group to chelate the active site zinc and may be classified broadly by this chelating group. Reported chelators include thiols,[6,7] carboxylic acids,[8] and phosphonic acids.[9] However, the most prevalent and potent chelators are hydroxamic acids.[3–5] The literature teaches that switching from hydroxamates to thiols is frequently accompanied by a 10 to 50× loss in potency.[6b]

We have discovered a new series of potent, low molecular weight compounds that preferentially inhibit MMP-8 and MMP-13 over MMP-1. This paper will outline the initial discovery and subsequent SAR optimization of this new class. Our initial lead was a simple sulfone hydroxamate that showed modest selectivity for MMP-13 over MMP-1. When we changed the chelator from a hydroxamate to a thiol we were surprised that the potency for MMP-13 was almost identical. (Table 1). Also noteworthy was the inherently high selectivity of these thiol sulfones. Selectivity in hydroxamic acid based chelators was achieved by placing large hydrophobic groups in P_1'.[10–12]

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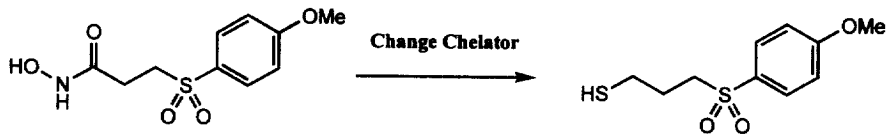


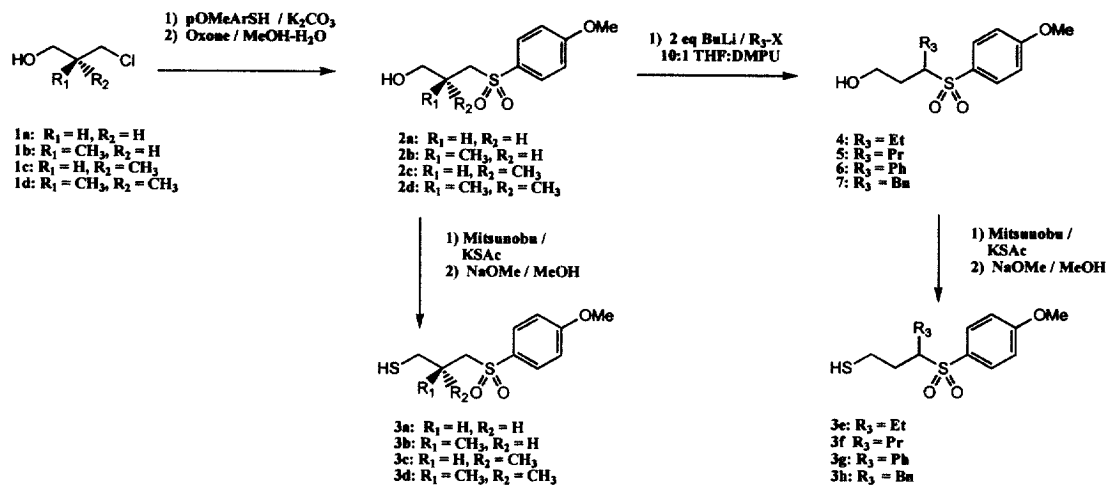
MMP-13 = 20 nM
MMP-1 = 500 nM

MMP-13 = 50 nM
MMP-1 = >10,000 nM

Table 1. Comparision of Hydroxamate vs Thiol

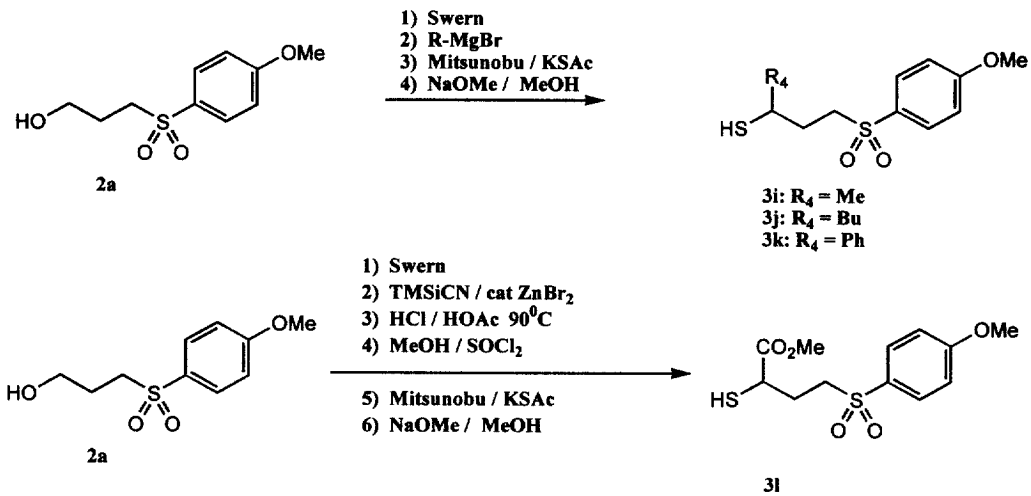
Chemistry

The lead thiol was prepared as shown in Scheme 1. The starting 3-chloropropanols were commercially available. Reaction with the appropriate thiophenol in the presence of potassium carbonate and DMF afforded the intermediate sulfide in high yield. Oxidation with Oxone® gave a quantitative yield of the sulfones **2a–d**. These were converted to the free thiols by Mitsunobu reaction with potassium thioacetate followed by hydrolysis to the desired product with base. The alkylation of sulfone **2a** was problematic until the conditions of Tanaka were adapted.[13] Treatment of the alcohol with 2 equiv of *n*-BuLi in THF/DMPU at –78 °C followed by addition of the electrophile afforded the products in good yield. In the reaction with benzyl bromide we saw small amounts of dialkylated product that was separated by flash chromatography.



Scheme 1. Preparation of β or γ substituted Thiol Sulfones

The phenyl substituted alcohol, **6**, was prepared via Michael reaction between *p*-methoxy thiophenol and *trans*-methyl cinnamate followed by LAH reduction and sulfur oxidation with Oxone®. Conversion to the free thiols **3e–h** was accomplished as described above. The preparation of α-substituted thiol sulfones is shown in Scheme 2. To introduce simple alkyl groups in the α-position, the alcohol was oxidized to the aldehyde under Swern conditions (Pyr-SO_3/NEt_3) and the aldehyde was reacted with the appropriate Grignard reagent. Conversion of the alcohol to the thiol was accomplished as described above to give thiols **3i–k**. A carboxyl moiety was introduced in the α position by reacting the aldehyde with trimethylsilylcyanide to give the O-silyl cyanohydrin. The crude cyanohydrin was hydrolyzed to the α-hydroxy acid using aqueous HCl/HOAc at 90 °C. The acid was converted to the methyl ester under standard Fisher conditions and the resulting alcohol was converted to the desired inhibitor **3l**. Thiol **3m** was prepared by reaction of 3-chloropropanol with *p*-phenoxythiophenol[14] followed by oxidation and conversion of the alcohol to the thiol as described in Scheme 1. Thiol **3n** was prepared by reacting 3-chloropropanol with *p*-fluorothiophenol, oxidation to the sulfone, followed by fluoride displacement with thiophenol in the presence of potassium carbonate and DMF at 60 °C. Conversion of the alcohol to the thiol led to **3n**.



Scheme 2. Preparation of α- substituted Thiol Sulfones

Discussion

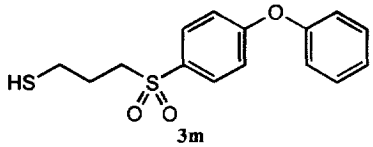
The data for the free thiols is shown in Table 2.[15] Introduction of alkyl (**3b** and **3c**) or dialkyl (**3d**) groups in the β position was detrimental to potency. Introduction of substituents γ to the thiol was more complex. Simple alkyl groups like ethyl and propyl (**3e** and **3f**, respectively) appear to increase potency equally for both MMP-13 and MMP-1, perhaps by orienting the (*p*-methoxy)phenyl ring in a more favorable confirmation in P_1'. Introduction of a benzyl side chain (**3h**) increases potency significantly for MMP-1. In fact, **3h** is essentially a broad spectrum inhibitor by our criteria.[16] Introduction of a phenyl side chain (**3g**) completely eliminates MMP activity. Introduction of α alkyl or aryl groups (**3i–k**) resulted in essentially no change from parent **3a**. The methyl ester **3l** gave a slight increase in potency.

The incorporation of bulkier groups in P_1' resulted in significant potency and selectivity for MMP-13 over MMP-1.[17] In fact thiols **3m** and **3n** are some of the most potent and selective MMP inhibitors yet reported. Especially noteworthy is their lack of chirality and relative simplicity.

In regards to other MMP's, thiol **3m** has an IC_{50} of 500 nM against stromelysin (MMP-3) and an IC_{50} of 4 nM against collagenase 2 (MMP-8). Thiol **3n** has an IC_{50} of 150 nM against stromelysin (MMP-3) and an IC_{50} of 36 nM against collagenase 2 (MMP-8). The pharmacokinetics and efficacy in animal models of osteoarthritis and cancer for this class of compounds will be reported in the future.

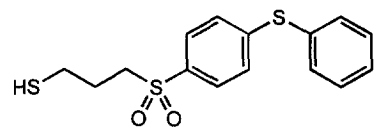
Table 2. Enzyme Data for Thiols 3a–n

Thiol (R)	MMP-13 IC_{50} (nM)	MMP-1 IC_{50} (nM)
3a (parent)	50	>10,000
3b (S-β Me)	475	>10,000
3c (R-β-Me)	250	5000
3d (β-DiMe)	700	>10,000
3e (γ-Et)	4	600
3f (γ-Pr)	6	1500
3g (γ-Ph)	1500	>10,000
3h (γ-Bn)	1	60
3i (α-Me)	32	8000
3j (α-Bu)	45	>10,000
3l (α-CO_2Me)	18	4000
3m	0.5	1500
3n	2	>10,000



3m

MMP-13 = 0.5 nM
MMP-1 = 1500 nM
MMP-3 = 500 nM
MMP-8 = 4 nM



3n

MMP-13 = 2 nM
MMP-1 = > 10,000 nM
MMP-3 = 150 nM
MMP-8 = 36 nM

Table 3. Optimized Thiol Sulfones

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14. *p*-Phenoxythiophenol was prepared from commercially available *p*-phenoxyphenol via the 3-step Newman sequence. See (a) Newman, M. S.; Karnas, H. *J. Org. Chem.* **1966**, 31, 3980. (b) Newman, M. S.; Hetzel, F. W. *Org. Synth.* **1988**, *VI*, 824.

15. Inhibitors were assayed against purified hMMP-13 and hMMP-1using a enzyme assay based on cleavage of the fluorogenic peptide; MCA-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2. This is similar to conditions described by C. G. Knight et al., *FEBS Lett.* **1992**, *296*, 263.

16. We call anything less than 100-fold selective a broad spectrum inhibitor.

17. (a) The optimization of P-1′ was carried out on a related series of thiol sulfonamides and will be communicated in the future. See DeCrescenzo, G. A.; Abbas, Z. S.; Freskos, J. N.; Getman, D. P.; Heintz, R.; Mischke; B. V.; **WO 9803166 A1**, Jan. 29, 1998. (b) Contrast the data for **3m** and **3n** with the para *n*-butoxy analogue of **3a** which had an IC_{50} of 55 nM against hMMP-13 and >10,000 nM against hMMP-1.