Sultam Hydroxamates as Novel Matrix Metalloproteinase Inhibitors

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Abstract: In this communication we describe the design, synthesis, and evaluation of novel sultam hydroxamates **4** as MMP-2, -9, and -13 inhibitors. Compound **26** was found to be an active inhibitor (MMP-2 IC_{50} = 1 nM) with 1000-fold selectivity over MMP-1 and good oral bioavailability (F = 43%) in mouse. An X-ray crystal structure of **26** in MMP-13 confirms the key hydrogen bonds and prime side binding in the active site.

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases belonging to the metzincin superfamily.[1] There are over 20 known MMPs, which include gelatinases, collagenases, and stromelysins.[2] The MMPs are involved in the proteolysis of the extracellular matrix, and they function to aid in the development, maintenance, and repair of tissues. Under normal conditions they are expressed in small amounts and are controlled by endogenous inhibitors. However, uncontrolled expression leads to tissue damage that has been linked to arthritis,[3,4] angiogenesis,[5] restenosis,[6] and multiple sclerosis.[7] This association has created an intense search for potent MMP inhibitors as potential therapeutics. Primarily, this search has focused on two main classes[8] of inhibitors: anti-succinates **1** and sulfonamides **2** and **3** (Scheme 1). The first clinical compounds were broad-spectrum inhibitors targeted mainly for cancer.[9] However, broad-spectrum MMP inhibition has been linked to side effects in the clinic,[10] and hence, we sought to find new templates that might offer different selectivity profiles upon optimization. From modeling the known scaffolds and examining their hydrogen bond network, we hypothesized that sultam **4** could be fashioned into a novel MMP inhibitor. Our model indicated that the pro-*S* sulfonyl (blue, Scheme 1) of sultam **4** could be positioned to overlay with the C(4) carbonyl of the anti-succinate class **1**. In doing so, the sultam sulfonyl is placed within hydrogen bond distance of the conserved leucine on the MMP backbone. To accommodate this hydrogen bond, the group connected to the nitrogen of the sultam (L−P1′, Scheme 1) would have a novel entry into the S1′ pocket of the MMPs, and it was this trajectory that we would need to optimize. In this communication, we describe the synthesis and evaluation of sultams **4** as novel MMP inhibitors.

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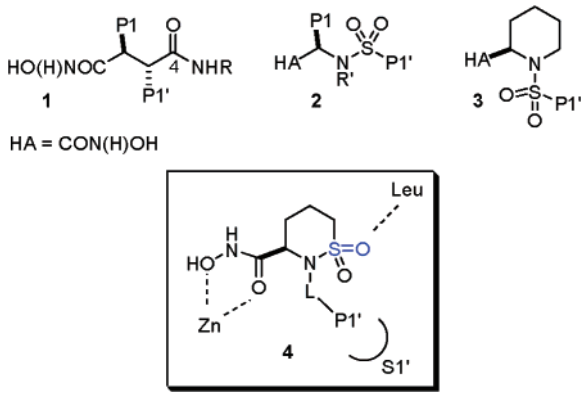
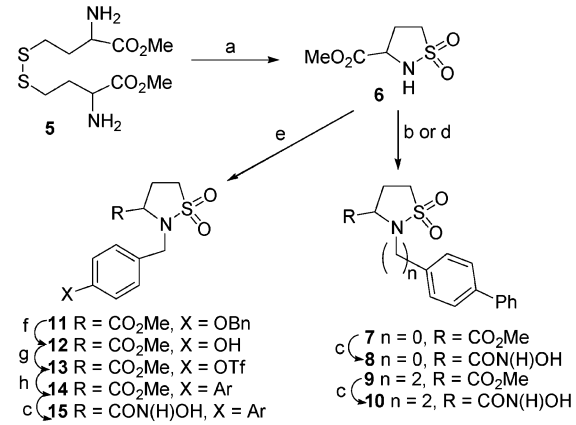
Scheme 1



Scheme 2[a]



[a] Reagents: (a) (i) Cl_2, EtOH/$CHCl_3$, 0 °C; (ii) Et_3N, $CHCl_3$, −5 °C, 75%; (b) 4-Ph−Ph−$B(OH)_2$, $Cu(OAc)_2$, Et_3N, 4 Å molecular sieves, CH_2Cl_2, 13%; (c) H_2NOH·HCl, KOH, MeOH, 30%; (d) DEAD, $P(Ph)_3$, $HOCH_2CH_2Ph$−Ph, THF, 88%; (e) K_2CO_3, $ClCH_2C_6H_4OBn$, DMF, Bu_4NI, 89%; (f) H_2, 5% $PdBaSO_4$, MeOH, quantitative; (g) Tf_2O, $(^iPr)_2NEt$, CH_2Cl_2, 77%; (h) $Pd(OAc)_2$, $ArB(OH)_2$, $P(Ph)_3$, K_2CO_3, toluene.

Scheme 2 outlines our initial synthetic entry into the sultams. Racemic homocystine **5** was oxidized to the sulfonyl chloride and cyclized as described by Luisi and Pinnen.[11] The resulting sultam **6** was arylated via copper-promoted chemistry[12] to afford **7**. Treatment of **7** with a basic hydroxylamine solution gave the hydroxamate target **8**.

Sultam **6** served as a common intermediate that could be alkylated to afford **9** or **11**. Biaryl **9** was converted into the target hydroxamate **10** in a manner analogous to **8**. Hydrogenation of **11** gave phenol **12**, which was converted into the aryl triflate **13**. Subsequent Suzuki reactions gave the biaryls **14**, which were converted to the hydroxamates **15** via standard chemistry. Homochiral six-membered sultams were synthesized according to Scheme 3. Alcohol **16**[13] was converted to the thioacetate **17** prior to chlorine oxidation,[14] selective *N*-Boc removal, and cyclization to sultam **18**. Chemistry similar to that described in Scheme 2 resulted in the hydroxamate **23**. This procedure was altered to accommodate the 4-pyridyl group of **26**, which was installed in one pot[15] through the aryl bromide **24**. Treatment of **25** with TFA afforded the carboxylate, which was

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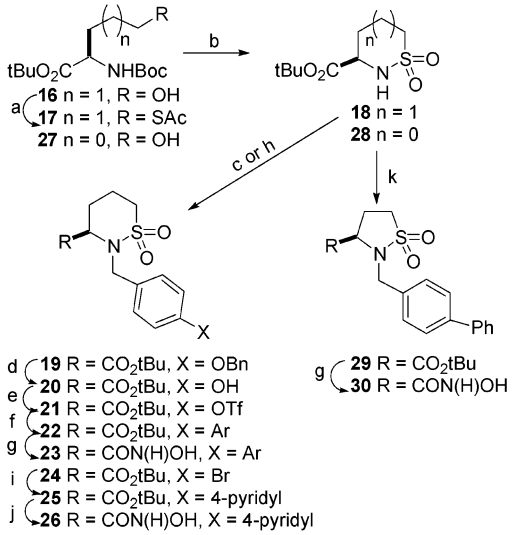
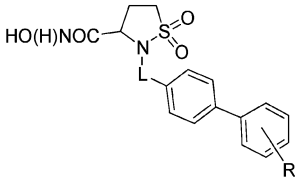
Scheme 3[a]



[a] Reagents: (a) AcSH, DIAD, PPh_3, THF, 57%; (b) (i) Cl_2, H_2O, (ii) 4 M HCl dioxane, THF; (ii) Et_3N, $CHCl_3$, 65%; (c) K_2CO_3, $ClCH_2C_6H_4OBn$, DMF, Bu_4NI, 96%; (d) H_2, 5% Pd/$BaSO_4$, MeOH, quantitative; (e) Tf_2O, $(^iPr)_2NEt$, CH_2Cl_2, 90%; (f) $Pd(OAc)_2$, $ArB(OH)_2$, PPh_3, K_2CO_3, toluene; (g) (i) TFA, CH_2Cl_2, (ii) *n*-PrOCOCl, NMM, DMF, −22 °C; (iii) $H_2NOH{\cdot}HCl$, NMM, DMF; (h) $BrCH_2C_6H_4Br$, K_2CO_3, DMF, 83%; (i) (i) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, THF, 80 °C, (ii) 4-bromopyridine·HCl, $PdCl_2$-(dppf), 2 M Na_2CO_3, THF, 80 °C; (j) (i) TFA, CH_2Cl_2, (ii) H_2NOBn, EDC, THF, (iii) H_2, 5% Pd/$BaSO_4$, MeOH; (k) K_2CO_3, Br−CH_2−4-Ph−Ph, DMF.

Table 1. In Vitro Evaluation of Five-Membered Sultams



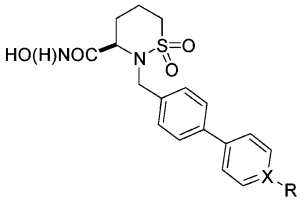
			K_i (nM)[a]			
compd	L	R	MMP-1	MMP-2	MMP-9	MMP-13
8		H	>4949	667	>2128	904
30[b]	CH_2	H	>4949	28.5	446.7	206
10	CH_2CH_2	H	>4949	433	702	1055
15a	CH_2	4-OMe	>4949	3.8	46.7	55
15b	CH_2	3,5-diCl	>4949	>3333	>2128	>5025
15c	CH_2	2-Me	>4949	>3333	>2128	>5025

[a] K_i values are an average from three determinations. Standard deviations are less than 15% in all cases. [b] Homochiral (*R*).

converted into the *O*-benzyl hydroxamate. Mild hydrogenation[16] of the *O*-benzyl hydroxamate afforded the key target **26**. Similar chemistry utilizing alcohol **27** and sultam **28** provided the homochiral five-membered target **30**.

The newly synthesized hydroxamates were evaluated[17] as MMP-2 and -9 inhibitors for their potential in cancer[5] and as MMP-13 inhibitors for osteoarthritis.[3] As previously mentioned, broad-spectrum MMP inhibitors have been linked to side effects in clinical trials; hence, we used a counterscreen of MMP-1 to assess initial selectivity. Our first task was to identify a group bonded to the sultam nitrogen capable of directing a substituent into the S1′ pocket of the MMPs. Several groups were attached, and an interesting trend was observed for biaryl groups (Table 1). Direct attachment of the biaryl to the sultam nitrogen (see **8**) displayed

Table 2. In Vitro Evaluation of Six-Membered Sultams



			K_i (nM)[a]			
compd	X	R	MMP-1	MMP-2	MMP-9	MMP-13
23a	C	OMe	938	0.4	0.9	1.2
23b	C	Cl	318	<3.3	<2.1	<5
23c	C	tBu	3166	3.2	8.5	<5
26	N		1085	1	10	3

[a] K_i values are an average from three determinations. Standard deviations are less than 15% in all cases.

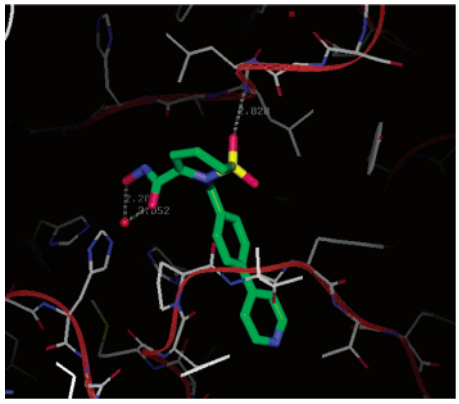


Figure 1. X-ray crystal structure of **26** cocrystallized in MMP-13.

moderate activity for MMP-2 (K_i = 667 nM) and MMP-13 (K_i = 904 nM). Addition of a methylene afforded **30**, which displayed good affinity for MMP-2 (K_i = 28.5 nM) over MMP-1, -9, and -13. Addition of a second methylene was detrimental because **10** lost substantial affinity for all the MMPs tested. With the benzyl group established as having the required trajectory into S1′, we turned our attention to substitution on the distal ring. The 4-methoxy substitution of **15a** provided a 7-fold increase in affinity for MMP-2 compared to **30** while still maintaining selectivity over MMP-1 (1000-fold) and MMP-9 and -13 (10-fold). However, both 3,5-substitution (**15b**) and 2-substitution (**15c**) afforded inactive compounds. Ring size was assessed, and the six-membered **23a** was found to be more potent against all the MMPs tested compared to the five-membered **15a** (Table 2). In addition to the potent affinity, **23a** still displayed at least 700-fold selectivity for MMP-2, -9, and -13 over MMP-1. As a result, we explored other substituents at the 4-position using the six-membered ring scaffold. The 4-position proved to be rather accommodating because electron-withdrawing and -donating substituents were potent inhibitors (see **23b**, **23c**, and **26** in Table 2) with excellent selectivity over MMP-1. In additional studies, **26** was also found to be selective for MMP-2, -9, and -13 over tumor necrosis factor-α converting enzyme (for **26** TACE K_i >1000 nM).

To better understand the binding of the sultams, **26** was cocrystallized in MMP-13. As shown in Figure 1, the hydroxamate makes the classical bidentate ligation to the active site zinc with the rest of the inhibitor

Table 3. Mouse Pharmacokinetic Data for **26**

mouse PK parameters	iv ($n = 3$)[a]	po ($n = 3$)[a]
dose (mg/kg)	10	30
Cl ((L/h)/kg)	5.6	
V_{ss} (L/kg)	7.3	
$T_{1/2}$ (h)	2.5	
AUC (nM·h)	3774	4895
F (%)		43

[a] Values are an average from three animals.

extending toward the prime side. As suggested by the SAR, the *N*-methylene of the sultam gives the biaryl the critical turn necessary to align the biaryls into the S1′ pocket. The crystal structure also confirms the hypothesis that the pro-*S* sulfonyl of the sultam can be positioned within the hydrogen bond distance of Leu-185. In fact, the conformation of the six-membered ring may help in the formation of this hydrogen bond when compared to the five-membered ring. The ring carbons appear to point toward the solvent-exposed area of the active site and are not involved in any contacts with the protein.

To assess the pharmacokinetics of the sultams, **26** was selected for a discrete mouse study. Mouse blood samples were collected serially and analyzed by LC/MS as shown in Table 3. Although clearance from the blood was high, **26** was orally bioavailable ($F = 43\%$).

In conclusion, sultam hydroxamates have been introduced as a new template for MMP inhibition. Proper alignment of the P1′ group necessitates having a benzyl alkylated sultam nitrogen. Biaryl groups with para substitution were found to be potent MMP inhibitors that spared MMP-1 inhibition. The crystal structure of **26** in MMP-13 indicates that the pro-(*S*) sultam sulfonyl is capable of a hydrogen bond to Leu-185. Initial mouse pharmacokinetics (PK) suggests that the sultam hydroxamates are orally bioavailable.

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Supporting Information Available: Experimental procedures and compound characterization data for target and intermediate compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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