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Abstract—A series of N-aryl isonipecotamide α-sulfone hydroxamate derivatives has been prepared utilizing a combination of solution-phase and resin-bound library technologies to afford compounds that are potent and highly selective for MMP-13.

Matrix metalloproteinases (MMPs) are zinc-dependent enzymes that are responsible for remodeling and degradation of all components of the extracellular matrix,[1,2] yet excessive activity of MMPs has been implicated in numerous disease states including cancer,[3,4] arthritis[5] and cardiovascular disease.[6-9] MMP inhibitors (MMPi's) have therefore been explored as therapeutic treatments to halt progression of various diseases.[10-12] The MMP family of enzymes includes at least 24 distinct mammalian isozymes, but MMP-13 in particular has been identified as a significant target since its upregulation has been implicated in cancer, osteoarthritis and cardiovascular disease.

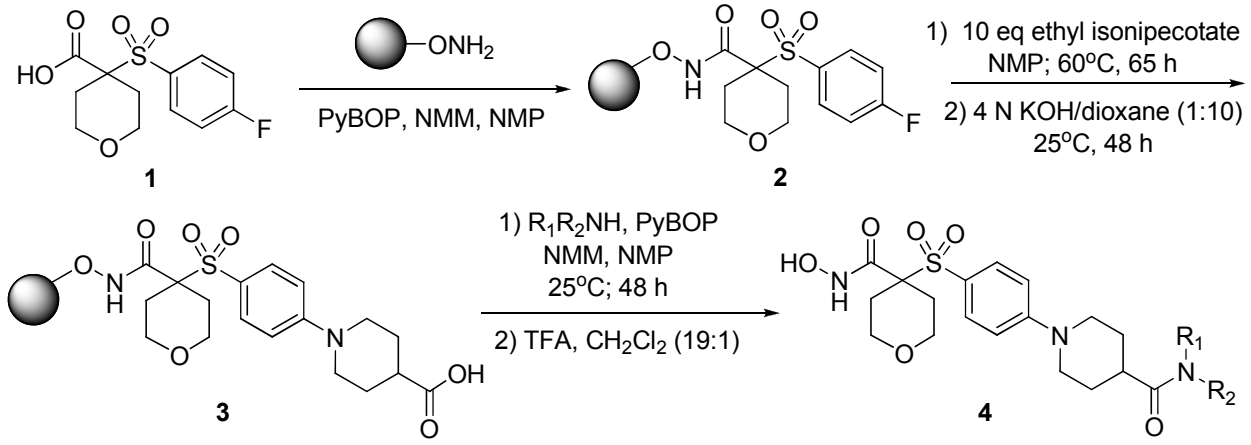
Treatment of patients with broad-spectrum MMPi's gives rise to stiffening of the joints referred to as musculoskeletal syndrome[9] (MSS). Inhibition of MMP-1 has been hypothesized to be the cause of MSS observed clinically with broad-spectrum inhibitors, and the broad-spectrum inhibitor marimastat induces musculoskeletal side effects in rats.[13] MMP-1 has long been suspected as a culprit whose inhibition plays a role in MSS. In addition, MT-1 MMP (MMP-14) knockout mice suffer connective tissue disease due to inadequate collagen turnover[14] and impaired endochondral ossification[15] reminiscent of joint lesions in MSS. We have therefore concentrated our efforts on potently inhibiting MMP-13 while sparing other MMPs to achieve joint safety, in particular MMP-1 and MMP-14, which we refer to as the dual-sparing hypothesis. MMP-13 selective α-carboxylic acids have been reported by Wyeth researchers.[16-18] Moderately selective pyrimidinetrione MMP-13 inhibitors have been reported that gave rise to fibroplasia in a 14-day rat study, but MMP-14 data was not reported.[19]

We previously described the synthesis and MMP inhibitory activity of β-sulfone hydroxamates[20-21] and aryl-linked isosteres[22-23] that potently inhibit MMP-2 and MMP-13 but spare MMP-1, and discovered that α-sulfone hydroxamates including **SC-276** are superior to the β-sulfones in both MMP-1 sparing enzyme profiles and ADME properties, and exhibit excellent oral antitumor efficacy *in vivo*.[24] MMP-1 sparing α-sulfone hydroxamates have also been

reported by the Wyeth group through modification of P1' substituents,[25, 26] and Wyeth researchers have also employed β-sulfones to attain potent and selective TACE inhibitors.[27, 28] Zhang et. al. of J&J have employed α-sulfone carboxylic acids as MMP-1 sparing gelatinase (MMP-2/9) inhibitors.[29] Our work in exploring modifications in the P' region toward further enhancing MMP-13 selectivity through interaction with the S_1' pocket has afforded a series of aryl piperidines and isonipecotamide derivatives that are highly selective for MMP-13 and sparing of both MMP-1 and MMP-14 as we report herein.

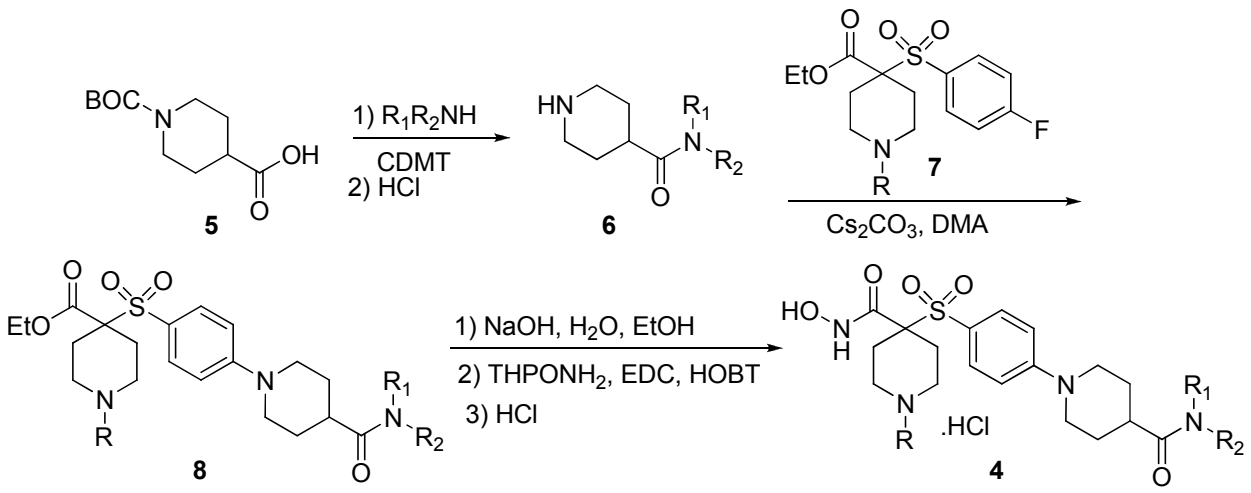
Isonipecotamide sulfone hydroxamates **4** in the α-tetrahydropyran series were prepared as outlined in Scheme 1. Carboxylic acid **1**[24] was coupled with the hydroxamate-containing modified Wang resin of Floyd[30] employing benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) as the coupling agent with N-methylmorpholine (NMM) in N-methylpyrrolidinone (NMP) to give polymer-bound aryl fluoride **2**. Nucleophilic aromatic substitution with a 10-fold excess of ethyl isonipecotate in NMP, and subsequent hydrolysis of the ethyl ester gave resin-bound carboxylic acid **3**. The polymer-bound acid was activated with PyBOP and reacted with the requisite amine to give the corresponding polymer-bound amides, which were liberated from the resin with TFA to afford isonipecotamides **4**.

Scheme 1. Synthesis of isonipecotamide sulfone hydroxamates in the α-tetrahydropyran series



Isonipecotamides **4** in the α-piperidine sulfone series were prepared by traditional solution-phase methodologies as outlined in Scheme 2. Ethyl isonipecotate N-*tert*-butylcarbamate **5**[31] was coupled with the requisite amine using 2-chloro-4,6-dimethoxy-1,3,5-trazine (CDMT) as a coupling reagent followed by deprotection with HCl to afford piperidine **6**. Nucleophilic aromatic displacement of aryl fluoride **7**[24] gave the aryl piperidine sulfone **8**. Hydrolysis of the ethyl ester, coupling with THP-protected hydroxylamine using EDC and HOBT followed by acidic deprotection afforded the hydroxamates **4** as the α-piperidine hydrochloride salts.

Scheme 2. Synthesis of isonipecotamide sulfone hydroxamates in the α-piperidine series



The inhibitory potencies of α-tetrahydropyranyl and α-piperidine sulfone hydroxamates **4a-w** versus MMP-2 and MMP-13 are summarized in Table 1 wherein the isonipecotic acid amide moiety was varied. Also shown in Table 1 is a selectivity ratio derived from dividing the IC_{50} at MMP-2 by that of MMP-13. Moderate potencies for MMP-13 were maintained, and single-digit nanomolar potency was attained for several analogs. All compounds had IC_{50} values of >10,000 nM for MMP-1 (not shown), thus selectivities for MMP-13 versus MMP-1 varied from >100X (**4n**) to >2000X. Selectivity ratios versus MMP-2 were generally in a range of 50 to 500, and as high as 1659 for **4f**. Allyl and propargyl derivatives **4a** and **4b** were moderately potent for MMP-13 with selectivities versus MMP-2 of approximately 85X. Selectivities rose for aralkyl substituted derivatives **4c**, **4d** and **4e** to nearly 400X for **4e**. 3,5-Dimethylpiperidine amide **4f** (mixture of cis and trans isomers) distinguished itself as the most potent for MMP-13 (IC_{50} = 4.4 nM) and the most selective versus MMP-2 as well (1659X). The corresponding α-piperidine N-methoxyethyl **4g** analog was prepared to improve aqueous solubility and ADME properties relative to **4f** (X = O). Surprisingly the MMP-13 potency for **4g** dropped to an IC_{50} of 50 nM, although α-piperidines were as potent as α-tetrahydropyrans in the broader-spectrum, MMP-1 sparing series,[24] while the potency for MMP-2 increased modestly to 1700 nM resulting in a 50-fold drop in selectivity versus MMP-2. *cis*-Dimethylmorpholine **4h** was 4X less potent than **4f**, suggesting that the trans isomer may be the more potent isomer in **4f**. Piperazine amides **4i**-**4n** suffered a loss of potency for MMP-13, particularly with the introduction of a basic amine leading to the least potent analog **4n**. N-Aryl piperazine amides **4o**-**4w** in general were more potent for MMP-13 with good selectivities versus MMP-2. Fluoro analogs **4o** and **4q** were among the most potent analogs (IC_{50} = 6.7 nM and 6.0 nM, resp.), along with 4-acyl derivative **4r**. The 2,4-dimethylphenyl analog **4s** maintained decent potency for MMP-13 (IC_{50} = 12.2 nM) and was less potent at MMP-2 leading to a selectivity of 460X. MMP-13 tolerated heterocyclic analogs **4t**-**4w** with a nitrogen in the 2-position of **4t** and **4u** (IC_{50} = 10.7 and 6.4 nM, resp.) with good selectivities (330X and 300X, resp.), whereas a nitrogen in the 3- or 4-position led to a loss of some potency and selectivity (**4v** and **4w**).

Table 2 summarizes inhibitory potency for 2,3-dimethylphenylpiperidine amides **4x**, **4y**, and **4z**. The α-tetrahydropyranyl (X = O) compound **4x** distinguished itself as both the most potent and selective of the isonipecotic amides, with an IC_{50} for MMP-13 of 4.0 nM and selectivity of 40X versus MMP-3, 1500X versus MMP-2, and >2500X versus MMPs-1, 8, 9, and 14.

Unfortunately, this compound was below the detection level when dosed orally in rats. The corresponding N-cyclopropyl and N-methoxyethyl piperidine analogs **4y** and **4z** were thus prepared, but the MMP-13 inhibitory potency for these compounds dropped 7X and 17X, respectively.

Table 3 shows the MMP inhibitory and rat PK data for aniline amide **4aa**, which had good potency for MMP-13 (IC_{50} = 9.0 nM) and very good selectivities versus both MMP-1 and MMP-14 (>1100X). However, exposure and half life in the rat were very poor after oral dosing, with a half life of less than one hour, and a BA of only 4%. Isonipecotamide hydroxamates described herein have demonstrated double-digit to single-digit potency for MMP-13 combined with very good selectivity versus MMP-1 (110 to 2500) and versus MMP-2 ranging from 30X to 1,500X. Compound **4x** exhibits >2,500X selectivity for MMP-13 versus both MMP-1 and MMP-14, hence we refer to this profile as dual-sparing (eg. MMP-13 potency while sparing both MMP-1 and MMP-14). Yet rat PK for **4aa** was disappointing, but not surprising with a high molecular weight of 544 a.u.[34] We therefore turned our attention to lower molecular weight species, while applying our learnings about P1´ manipulations toward optimizing MMP-13 selectivity and ultimately to MMP-1/14 dual-sparing profiles with lower MW and fewer reduce rotatable bonds as described in the subsequent publication.[35]

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