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MMP-13 Selective Isonipecotamide α-Sulfone Hydroxamates

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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\(^20-22\) 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 \textit{in vivo}.\(^24\) MMP-1 sparing α-sulfone hydroxamates have also been
reported by the Wyeth group through modification of P1’ substituents, and Wyeth researchers have also employed β-sulfones to attain potent and selective TACE inhibitors. Zhang et. al. of J&J have employed α-sulfone carboxylic acids as MMP-1 sparing gelatinase (MMP-2/9) inhibitors. Our work in exploring modifications in the P’ region toward further enhancing MMP-13 selectivity through interaction with the S1’ 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 in the α-tetrahydropyran series were prepared as outlined in Scheme 1. Carboxylic acid 1 was coupled with the hydroxamate-containing modified Wang resin of Floyd 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. 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 was coupled with the requisite amine using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) as a coupling reagent followed by deprotection with HCl to afford piperidine. Nucleophilic aromatic displacement of aryl fluoride gave the aryl piperidine sulfone. 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, 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. 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.

References and Notes

35. *back-to-back communication following this manuscript – insert reference when available.*