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Stephen A. Kolodziej
Susan L. Hockerman
Gary A. DeCrescenzo
Joseph J. McDonald
Grace E. Munie

See next page for additional authors

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This is a pre-publication author manuscript of the final, published article.

Recommended Citation
Authors
Stephen A. Kolodziej, Susan L. Hockerman, Gary A. DeCrescenzo, Joseph J. McDonald, Grace E. Munie, Theresa R. Fletcher, Nathan Stehle, Craig Swearingen, and Daniel Becker

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MMP-13 Selective Isonipecotamide α-Sulfone Hydroxamates

Stephen A. Kolodziej, Susan L. Hockerman, Gary A. De Crescenzo, Joseph J. McDonald, Debbie A. Mischke, Grace E. Munie, Theresa R. Fletcher, Nathan Stehle, Craig Swearingen and Daniel P. Becker

Departments of Medicinal Chemistry and Pharmacology, Pfizer Research & Development, 700 Chesterfield Village Parkway, St. Louis, MO 63198, USA

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, yet excessive activity of MMPs has been implicated in numerous disease states including cancer, arthritis and cardiovascular disease. MMP inhibitors (MMPi’s) have therefore been explored as therapeutic treatments to halt progression of various diseases. 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 (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. 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 and impaired endochondral ossification 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. 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.

We previously described the synthesis and MMP inhibitory activity of β-sulfone hydroxamates and aryl-linked isosteres 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. 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 4 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. 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 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 4\(y\) and 4\(z\) 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 4\(aa\), 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 4\(x\) 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 4\(aa\) 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.\(^{35}\)

References and Notes
35. back-to-back communication following this manuscript – insert reference when available.