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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[20,21] 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

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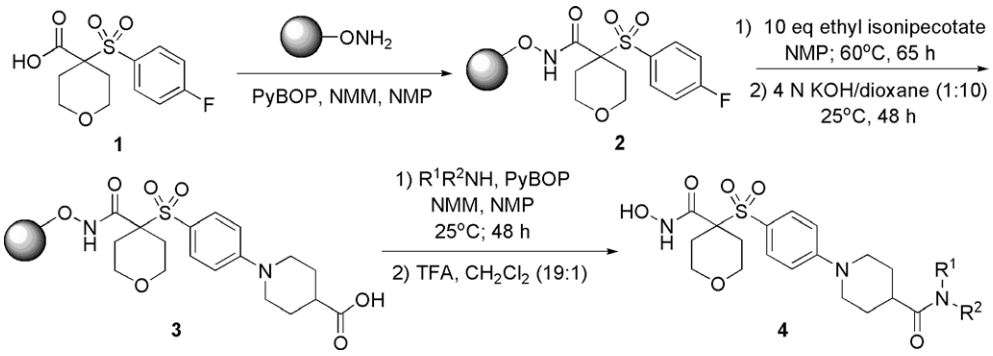


Scheme 1. Synthesis of isonipecotamide sulfone hydroxamates in the α-tetrahydropyran series.

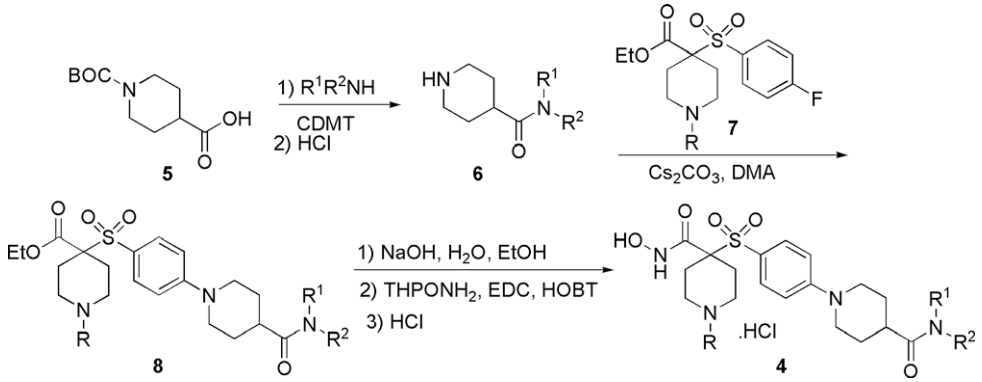
with PyBOP and reacted with the requisite amine to give the corresponding polymer-bound amides, which were liberated from the resin with TFA to afford isonipecotamides **4**.

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.

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 50–500, 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 and 6.0 nM, respectively), 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, respectively) with good selectivities (330X and 300X, respectively), whereas a nitrogen in the 3- or 4-position led to a loss of some potency and selectivity (**4v** and **4w**).

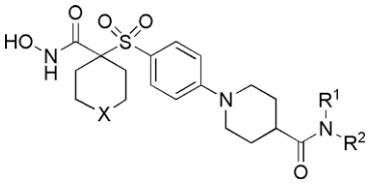
Table 2 summarizes inhibitory potency for 2,3-dimethylphenylpiperidine amides **4x**, **4y**, and **4z**. The α-tetrahydropyranyl (X = O) compound **4x** distinguished itself as both the most potent and selective of the isonipecotic amides, with an IC_{50} for MMP-13 of 4.0 nM and selectivity of 40X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



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

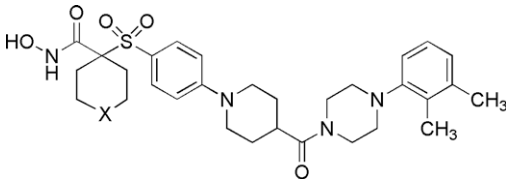
Table 1
MMP inhibitory potency of isonipecotamide α-tetrahydropyranyl and α-piperidine sulfone hydroxamates **4a–w**[a]



Compd	X	NR^1R^2	IC_{50} (nM) at MMP-X[a]		Selectivity ratio 2/13
			2	13	
4a	O	Allyl(methyl)amino	2900	35	83
4b	O	Methyl(prop-2-ynyl)amino	2100	24.5	86
4c	*N*-Cyclopropyl	Benzyl(methyl)amino	3500	20	175
4d	O	3,4-Dihydroisoquinolin-2(1H)-yl	2100	9	233
4e	O	6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl	2400	6.2	387
4f	O	3,5-Dimethylpiperidin-1-yl	7300	4.4	1659
4g	N-CH_2CH_2OMe	3,5-dimethylpiperidin-1-yl	1700	50	34
4h	O	*cis*-2,6-Dimethylmorpholin-4-yl	>10K	18.1	552
4i	O	4-Acetylpiperazin-1-yl	2500	50	50
4j	O	4-Isopropylpiperazin-1-yl	5500	28	196
4k	O	4-(2-Methoxyethyl)piperazin-1-yl	7000	45	156
4l	O	4-Phenethylpiperazin-1-yl	900	25.1	36
4m	O	4-(2-Hydroxyethyl)piperazin-1-yl	6000	40	150
4n	O	4-(2-(Dimethylamino)ethyl)piperazin-1-yl	>10,000	90	>111
4o	O	4-(2-Fluorophenyl)piperazin-1-yl	1400	6.7	209
4p	O	4-(2-Methoxyphenyl)piperazin-1-yl	4500	18.0	250
4q	O	4-(4-Fluorophenyl)piperazin-1-yl	1600	6.0	267
4r	O	4-(4-Acetylphenyl)piperazin-1-yl	700	6.7	104
4s	O	4-(2,4-Dimethylphenyl)piperazin-1-yl	5600	12.2	459
4t	O	4-(Pyridin-2-yl)piperazin-1-yl	3600	10.7	336
4u	O	4-(Pyrimidin-2-yl)piperazin-1-yl)	1600	6.4	250
4v	O	4-(Pyridin-4-yl)piperazin-1-yl	1750	30	58
4w	O	4-(Pyrazin-2-yl)piperazin-1-yl	900	26.8	34

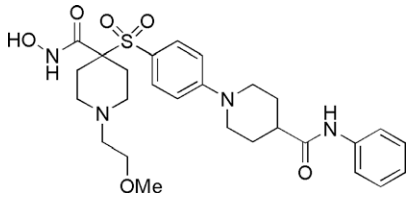
[a] MMP-1 IC_{50} >10,000 nM for all compounds.

Table 2
MMP inhibitory potency of isonipecotamide α-sulfone hydroxamates **4x**, **4y**, and **4z**



Compd	X	IC_{50} (nM) at MMP-X						
		1	2	3	8	9	13	14
4x	O	>10,000	6000	160	>10,000	>10,000	4.0	>10,000
4y	*N*-Cyclopropyl	>10,000	6350	550	9400	>10,000	27.7	>10,000
4z	NCH_2CH_2OMe	>10,000	400	—	—	—	70	—

Table 3
MMP inhibitory potency and rat PK data of isonipecotamide α-sulfone hydroxamate **4aa**



Compd	*clog P*	IC_{50} (nM) at MMP-X							Rat PK			
		1	2	3	8	9	13	14	C_{max}	C_{6h}	$t_{1/2}$ (h)	BA (%)
4aa	1.0	>10,000	400	370	>10,000	1230	9.0	>10,000	1490	20	0.83	4.2

(>1100X). However, exposure and half life in the rat were very poor after oral dosing, with a half life of less than 1 h, 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 (110–2500) and versus MMP-2 ranging from 30X to 1500X. Compound **4x** exhibits >2500X selectivity for MMP-13 versus both MMP-1 and MMP-14, hence we refer to this profile as dual-sparing (e.g., 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.[32] 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.[33]

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