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MMP-13 Selective α -Sulfone Hydroxamate Flexible Chain P1' Amides

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Abstract: Continuing our interest in designing compounds preferentially potent and selective for MMP-13, we report on a series of hydroxamic acids with a flexible amide P1' substituents. We identify an amide which spares both MMP-1 and -14, and shows >500 fold selectivity for mmp-13 vs. MMP-2 and -8.

Matrix Metalloproteinases (MMPs) are a family of about 27 zinc-dependent enzymes responsible for the turnover of collagen in connective tissue. There are a variety of disease states where degradation of collagen contributes to the pathology, specifically, in osteo- and rheumatoid arthritis; in tumor angiogenesis and metastasis; and in post-MI cardiovascular remodeling.¹ In spite of the promise that modulation of MMP activity offers, the road from proof of concept to pharmacy shelves has been a long one. Clinical compounds often induce a dose-limiting joint-stiffening often referred to as musculoskeletal syndrome (MSS).

It has been hypothesized that inhibition by drug candidates of MMP-1, a constitutive enzyme involved in the turnover of type II collagen, contributes to MSS.^{2a} Sparing MMP-1 may not be sufficient. In our earlier research we saw that dosing with the MMP-1 sparing hydroxamate **1** (SC-276, **Figure 1**) eventually led to joint stiffening.^{2b} MT1-MMP (MMP-14) may also play a role in MSS, since it has been observed that MMP-14 knockout mice suffer from joint lesions reminiscent of the changes in MSS.³ The actual situation may be even more complex; MMP inhibitors that spare both MMP-1 and -14 may bind to members of the structurally-related ADAMs family (A Disintegrin And Metalloprotease),⁴ leading to undesired joint effects.

An alternative approach toward realizing efficacious MMP inhibitors with reduced side effects is to focus on optimizing the inhibition of the single MMP isoform that should confer the most therapeutic benefit, reducing the probability of off-target protease inhibition. MMP-13 is an attractive isoform to pursue; MMP-13 rapidly degrades type II collagen and is associated with pathology. The isoform is upregulated in osteoarthritic joints and in cancer.⁵ Structural studies show that MMP-13 differs from other MMP's in the depth of its S1' pocket, suggesting that lengthier inhibitors may confer selectivity.

With this in mind, we previously reported a series of rigid piperidino- ketones (compound **2**, **Figure 1**) with lengthier P1' subunits and, with optimization, we achieved significant selectivity for MMP-13 vs. other MMP isoforms.^{6,7} Although potent and selective, ketones like **2** exhibited poor PK, so we endeavored to improve their ADME properties, in part, though reduction of

molecular weight. Conceptually dissecting the piperidine ring in compound **2** led to acyclic-chain analogs such as ketone **3a** (**Figure 1**).

The synthesis of ketone **3a** and related ketones (e.g. **3b**, **Scheme 1**) proceeded from aryl fluoride **4**,⁸ which was reacted with an omega benzyloxy 1-alkanol. The benzyl alcohol could be cleaved by hydrogenation and the resulting alcohol oxidized to a carboxylic acid. This acid, **6**, was converted using EDC coupling to a Weinreb amide⁹ and the t-butyl ester was treated with TFA to liberate the acid on the left hand side of the molecule, and this acid was coupled with THPONH₂. Excess aryl Grignard and subsequent treatment with HCl led to the final product, **3b**. Similar straightforward chemistry could be used to arrive at amides like **16a**.

Isomeric amides (**Scheme 2**) could be obtained using, for example, *tert*-butyl N-(3-hydroxypropyl)carbamate, which could be carried on to amine **9**. Amine **9** was converted to amide analogs **10**, and on to final hydroxamic acids **12a**.

We synthesized over 500 extended chain amides and ketones in our MMP-13 program and the findings for selected analogs are summarized in Table 1. Isonipecotate **2** demonstrates excellent selectivity for MMP-13 vs. the other MMP isoforms tested. The direct open-chain analogs of **2**, ketones **13**, **14**, and **3a**, which differ in connecting chain length, are each more potent toward MMP-13 than isonipecotate **2**. Compounds **14** and **3a** achieve encouraging selectivity ratios for MMP-13 vs. MMP-8, -9, -1, and -14, but exhibit poor selectivity with respect to MMP-2.

We looked at different linkers. Ether-linked compounds, like **17**, lacked MMP-13/-2 selectivity. Amide analogs **15a** and **16** show a significant diminution of selectivity, with **16** being essentially equipotent for -8 and -13. N-Methylation, to alter the steric environment, did not improve the ratios, as can be seen from **15c** and **15d**.

The benzamides of Scheme 2 looked significantly more attractive; compound **12b**, for example, is potent for MMP-13, but unlike some of our earlier compounds spares MMP-2. Compounds **12a** and **12c** also had desirable profiles. Conjugation of the amide π system into the aryl ring may diminish the conformational mobility of these amides vs. the amides of Scheme 1 (e.g. **12c** vs **15a**) and this might account for the improved selectivity of the latter series. In general, the electronics of ring substitution did not have a pronounced effect on potency/selectivity, but more hindered analogs, such as **12d**, saw a drop off in activity. We also looked at "non-aryl" amides, including **12e** and **12f**, and the compounds tested showed reduced potency and/or selectivity.

Benzamides like **12a** and **12c** became the focus of further study, and, while we achieved meaningful levels of MMP-13 selectivity, we did not find amides that had both high potency and acceptable PK properties. Compound **12a** had a half-life in rats of 0.58 h (BA 1.5%), presumably due to *in vivo* amide hydrolysis, and that was typical of the series. To address this issue, non-

hydrolyzable bioisosteric replacements for the amide linkage were sought, as reported in the following Letter.

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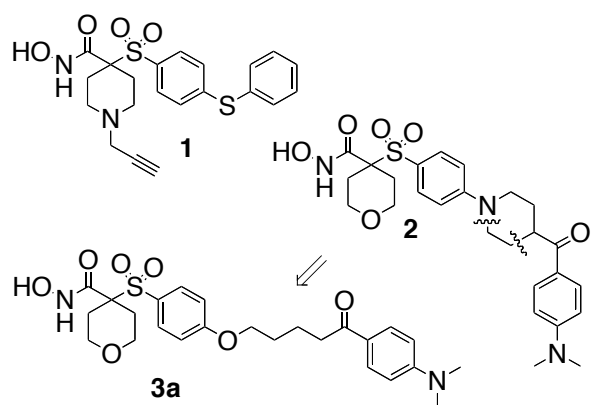
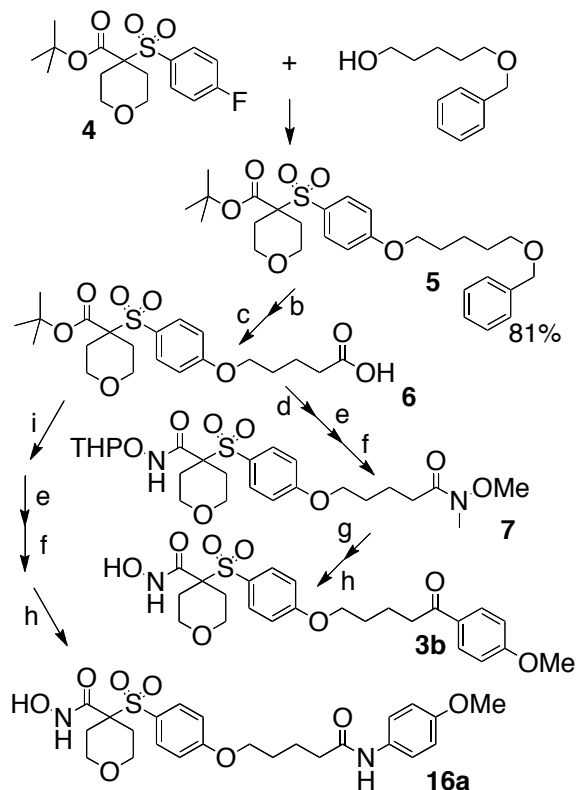


Figure 1. MMP inhibitors. Compound **1** spares MMP-1; Compounds **2** and **3** are MMP-13 selective.

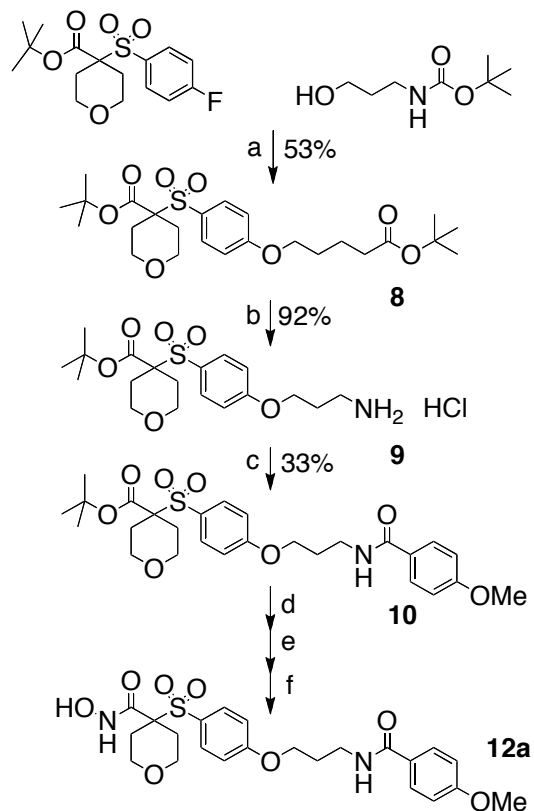


Scheme 1. Reagents and Conditions: (a) X (1.05 eq), NaH 1.2 (eq), 0°C-r.t., 4 h. (b) 5% Pd/C (wet), 80 psi, THF, 1.5 h quant. (c) 2.5% RuCl₃, NaIO₄ (3 eq), CCl₄, water, quant (d) triethylamine (6.0 eq), N-hydroxybenzotriazole (1.5 eq), HN(Me)OMe (3.0 eq), EDC (1.4), DMF, 16 h (e) trifluoroacetic acid, triturate (f) triethylamine (2.1 eq), N-hydroxybenzotriazole (3.0 eq), THPONH₂ (3.0 eq), EDC (1.2 eq), DMF, 3.5 h 40°C, rt 16 h (g) 4-(MeO)PhMgBr (5 eq), THF, 0°C-rt overnight, then NH₄Cl (h) 4N HCl, dioxane, MeOH, triturate (i) N-methylmorpholine (2.1 eq), N-hydroxybenzotriazole (1.2 eq), anisidine (1.5 eq), EDC (1.5 eq), DMF, rt.

Table 1: MMP selectivity of studied compounds

#	N	Y	hMMP IC ₅₀ (nM) ^a			
			-2	-8	-9	-13
1	-	-	0.33	1.8	1.5	<1.0
2	-	-	4000	>10k	>10k	8.0
3a	4		35	140	1100	0.4
12a	3		550	900		1.6
12b	3		1100	1000		2.0
12c	3		360	140	2200	0.66
12d	3		940	700		8.0
12e	3		650	3100		8.2
12f	3		450	1200		30
13	2		16	120		0.9
14	3		18	170	930	0.2
15a	3		10	100	960	1.7
15b	3		2.5	31	23	0.3
15c	3		11	6.7	180	0.2
15d	3		270	49	380	3.3
15e	3		170	800	670	1.2
16	4		1.8	2.6	500	1.8
17	4		6.6	67		0.9

a. For each compound, MMP-1 and MT1-MMP > 5000, except for 1, where MT1-MMP = 8 nM.



Scheme 2. Reagents and Conditions: (a) *tert*-butyl N-(3-hydroxypropyl)carbamate (1.1 eq), NaH (1.2 eq), DMF, 0°C, 18 h (b) 4N HCl/dioxane, 1 h (c) DMF, triethylamine (1.2 eq), anisoyl chloride (1.2 eq) (d) trifluoroacetic acid, 3 h, conc. at 50°C, quant. (e) N-methylmorpholine (2.1 eq), N-hydroxybenzotriazole (1.2 eq), THPONH₂ (1.5 eq), EDC (1.5 eq), DMF, 3 days (f) 4N HCl. dioxane, MeOH, 1 h, conc., triturate

